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MEDIAL DEGENERATION OF THE AORTA AS SEEN IN TWELVE CASES OF DISSECTING ANEURYSM

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Degenerative lesions in the media of the aorta have been described in cases of dissecting aneurysm for many years. Among the pioneers were Moriani,[1] Shennan and Pirie [2] and Furno.[3] Interest in the subject was given renewed vigor by Gsell,[4] who carried over to the aorta Wiesel's [5] observation of muscle necrosis in peripheral vessels. This was immediately followed by contributions from Erdheim,[6] who introduced a new concept—medial degeneration by mucoid degeneration rather than by antecedent muscle necrosis. Since then many others have added their efforts to the solution of the problem (Cellina;[7] Levinson;[8] Wolff;[9] Neuberger;[10] Moritz;[11] Klotz and Simpson;[12] Weise [13]).

The observations of Gsell were of particular importance. He described a form of medial degeneration which apparently began as focal necrosis of muscle. This was followed later by disintegration of elastic tissue and collagen, resulting in the formation of gaps. Healing, if it

From the laboratories of pathology of St. Vincent's Hospital and Bellevue Hospital and the Office of the Chief Medical Examiner.

1. Moriani, G.: Virchows Arch. f. path. Anat. **202**:283, 1910.
2. Shennan, T., and Pirie, J. H. H.: Brit. M. J. **2**:1287, 1912.
3. Furno, A.: Arch. di pat. e clin. med. **3**:26, 1924.
4. Gsell, O.: Virchows Arch. f. path. Anat. **1**:270, 1928.
5. Wiesel, J.: Ztschr. f. Heilk. **8**:69, 1907.
6. Erdheim, J.: (*a*) Virchows Arch. f. path. Anat. **273**:454, 1929; (*b*) **276**: 187, 1930.
7. Cellina, M.: Arch. ital. di anat. e istol. pat. **2**:1105, 1931; Virchows Arch. f. path. Anat. **280**:65, 1931.
8. Levinson, B.: Virchows Arch. f. path. Anat. **282**:1, 1931.
9. Wolff, K.: Virchows Arch. f. path. Anat. **285**:1, 1932; **289**:1, 1933.
10. Neuberger, K.: Ztschr. f. Kreislaufforsch. **24**:169, 1932.
11. Moritz, A. R.: Am. J. Path. **8**:717, 1932.
12. Klotz, O., and Simpson, W.: Am. J. M. Sc. **184**:455, 1932.
13. Weise, W.: Beitr. z. path. Anat. u. z. allg. Path. **93**:238, 1934.

occurred, took place by the appearance of loose scar, very poor in collagen. Most striking was the absence of cellular reaction.

While in his first report Erdheim [6a] concurred with Gsell, in his second contribution [6b] he introduced a new form of medial degeneration, called by him "medionecrosis aortae idiopathica cystica." In this instance he believed that the disease began with the accumulation of abnormal quantities of mucoid material in the media, spreading as it increased beyond the confines of single interlamellar spaces until with the dissolution of previously normal muscle, collagen and elastic tissue, mucoid-filled spaces remained. Healing occurred by the formation of loose, nonvascularized scars or by regeneration of the original elements. At no time in the entire process was an inflammatory mechanism evident. Intima, adventitia and vasa vasorum played no visible role. In subsequent reports other students have described the medionecrosis of Gsell or the mucoid degeneration of Erdheim without clearly differentiating between the two.

It is the purpose of this paper to present a study of medial degeneration as encountered in 12 selected cases of dissecting aneurysm of the aorta. Eleven others were discarded either because tissue for study was no longer available or because the condition was complicated by another disease, such as syphilis or bacterial endocarditis. In 9 of the 12 cases the heart and aorta had been saved. In the remaining 3 cases the material available included the ruptured intima, making it possible to study the wall of the vessel in this region. In 10 cases the dissection and intimal rupture were recent, in the remaining 2, long standing. The intimal rupture was supravalvular in 10 cases and at the arch in 2.

METHOD OF STUDY

In 8 cases the entire aorta from the root to and including the arch was cut into serial blocks. Beyond, representative sections were taken every 3 to 4 cm. When these were cut transversely, they included the entire circumference of the vessel; when cut longitudinally, they extended from root to arch. Only in case 12 was it found necessary to make the sections small. However, enough was taken from representative locations to make the inclusion of the case in the series justifiable. Blocks were also cut from the myocardium and coronary arteries and from the valves when the latter were visibly diseased. The following stains were employed: hematoxylin and eosin, Mallory's phosphotungstic acid–hematoxylin, Weigert's stain for elastic tissue, Van Gieson's stain, Masson's trichrome stain. In some cases the Foot and Foot stain for reticulum was used. In a single instance the Von Kossa stain aided in demonstrating calcium. Thionine and cresylecht violet were found useful for visualization of mucoid substances.

In order that the distribution of lesions might be studied better, a map of the aorta was made in each case and the different types of lesions were charted on it in code. Thus it was possible to note at a glance their number, distribution and relation to each other and to the point of intimal rupture (fig. 1).

RESULTS

In every case destructive noninflammatory lesions were found in the media of the aorta. The simplest and most common type, present in 10 of 12 cases, was characterized by focal loss of muscle (fig. 2*A*) and crowding together of elastic laminae. In only 3 of these 10 instances was it possible to recognize anuclear remains of muscle cells.[14] Lesions

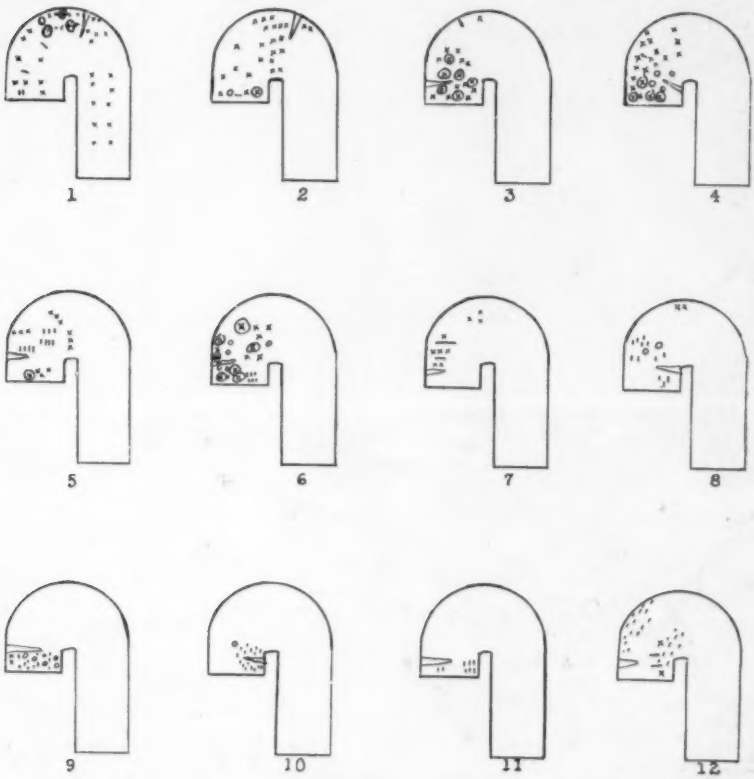

Fig. 1.—Diagrams of aortas from 12 patients with dissecting aneurysm, showing distribution of simple muscle loss (x), muscle and elastic tissue loss (circled x), cyst formation (o), scar formation (-) and medical regeneration (‴) and the location of the intimal rupture (>).

of this type were found chiefly in the middle and inner thirds of the aorta from root to isthmus, adjacent to and beyond the region of intimal rupture, in dissected portions (cases 3, 4, 5, 6, 7, 8, 9 and 12) and non-dissected portions (cases 1 and 2) of the aorta. In case 1 only were they found in the descending portions as well. The severity as measured by

14. This finding is mentioned because it is used by Gsell as indicating necrosis.

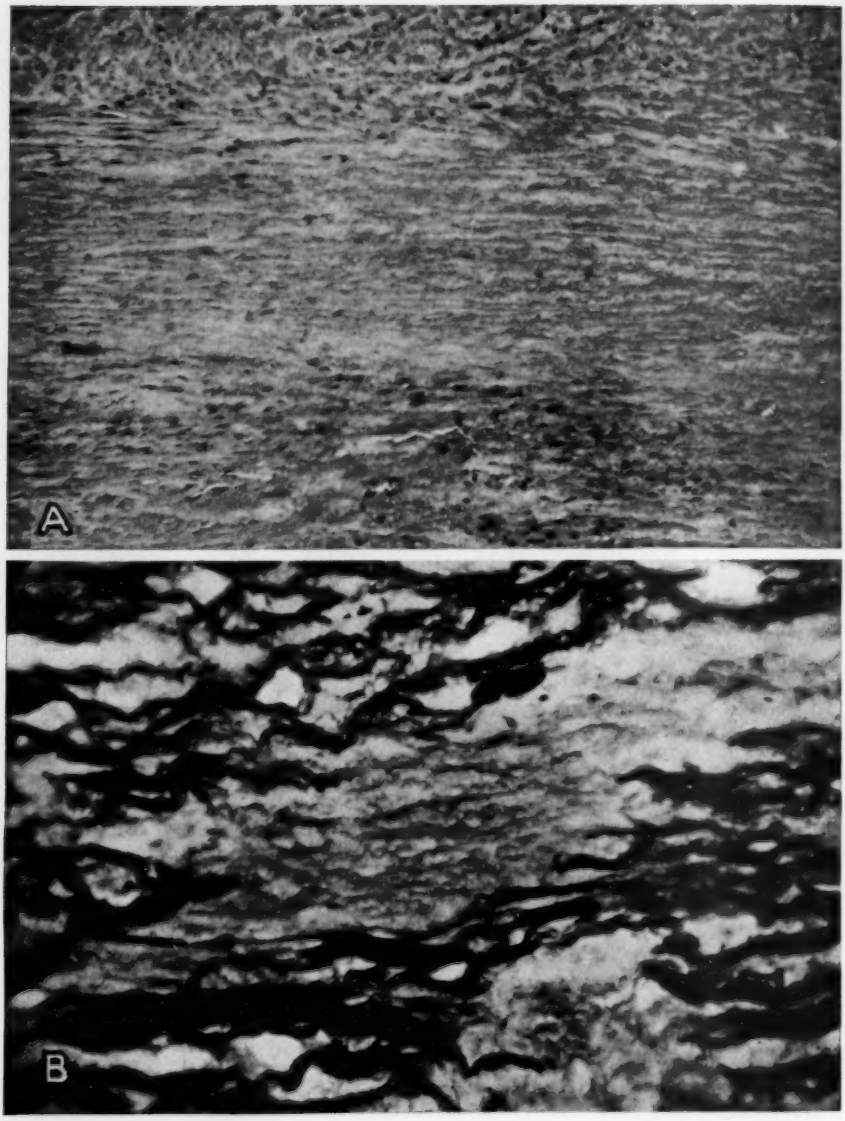

Fig. 2.—*A*, simple muscle loss; hematoxylin-eosin stain. Note the complete absence of cells in the midzone. *B*, more advanced degeneration; Weigert's stain for elastic tissue. In addition to the disappearance of muscle in this area, there are a thinning and loss of staining of the elastic lamellae.

size and number varied in different cases, being extreme in 4 cases (1, 2, 3 and 4), moderate in 3 (5, 6 and 7), mild in 3 (8, 9 and 12) and absent in 2 (10 and 11).

In 8 cases the lesions were of a more advanced type, characterized not only by loss of muscle but by degeneration of elastic and collagenous tissue as well. These tissues were found in all stages of disintegration, from thinning and loss of the tinctorial properties of elastic lamellae (fig. 2 *B*) to the completion of the process with formation of mucoid-filled cavities bordered by normal media (fig. 3 *A*).

The size of the lesions of this type varied. The damage was insignificant in some instances and in others it was visible on holding elastic tissue preparations up to the light. The largest lesion measured 3 to 4 mm. long and occupied the entire width of the media. These lesions were moderately numerous in 6 cases (1, 3, 4, 6, 8 and 9), scant in 2 (2 and 10) and absent in 4 (5, 7, 11 and 12). Their distribution was more or less similar to that of simple muscle loss with the exception that in no case was a lesion of the advanced type present in the descending aorta. In 7 cases this type was found in the same vessel in which simple muscle loss was present. The predominance of each type in any one aorta varied. In 2 cases (1 and 2), the simple type predominated, in 2 others (3 and 4) both were equally conspicuous, and in 3 the more advanced lesion overshadowed the other (6, 8 and 9).

The third [15] type of lesion to be described was found in 8 cases (1, 5, 6 and 8 to 12). Its chief characteristic was the presence of variable numbers of muscle cells, scant or more numerous than normal, occupying areas devoid of elastic laminae (fig. 3 *B* and 4 *A*). In some lesions the muscle cells apparently lay free in mucoid material; in others they were enmeshed in a network formed by loosely arranged collagenous tissue (fig. 3 *B*). This type of lesion could be detected in hematoxylin-eosin preparations by the unusual direction of the long axes of the muscle cells, which ran perpendicularly or obliquely to muscle cells of adjacent normal media. In 2 cases (5 and 6) lesions of this type were moderately prominent; in 5, markedly so, and in 1, scant (1). In every instance they were observed in the lower half of the ascending aorta only. Such lesions constituted almost the sole abnormality in 3 cases (10, 11 and 12). In 3 others (5, 8 and 9) advanced degenerative changes were equally conspicuous. In the remaining 2 cases (1 and 6) the third type sank into insignificance alongside destructive lesions.

A fourth type of lesion, present in scant numbers in 4 cases, must be mentioned. It consisted of loosely constructed small fibrous scars

15. As I lean toward the theory of Erdheim, who felt that the lesion represented a regenerative phenomenon, I have captioned it in figure 1 as "medial regeneration."

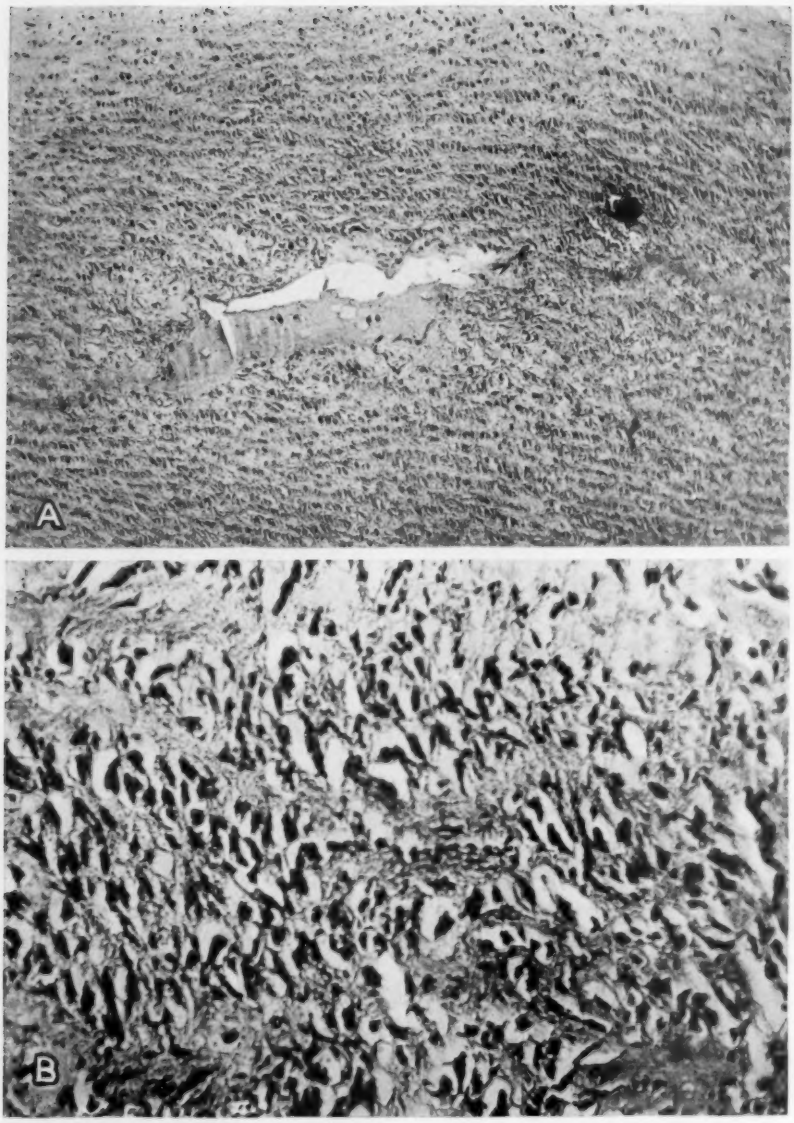

Fig. 3.—*A*, mucoid-filled cyst, surrounded by normal media; hematoxylin-eosin stain. This is an end stage of the process depicted in figure 2. *B*, area of regeneration; phosphotungstic acid-hematoxylin stain; high power magnification. Note that muscle cells are numerous and irregularly arranged. The supporting stroma consists of a loose collagen meshwork. Elastic tissue is not present. (See fig. 4 *A*.)

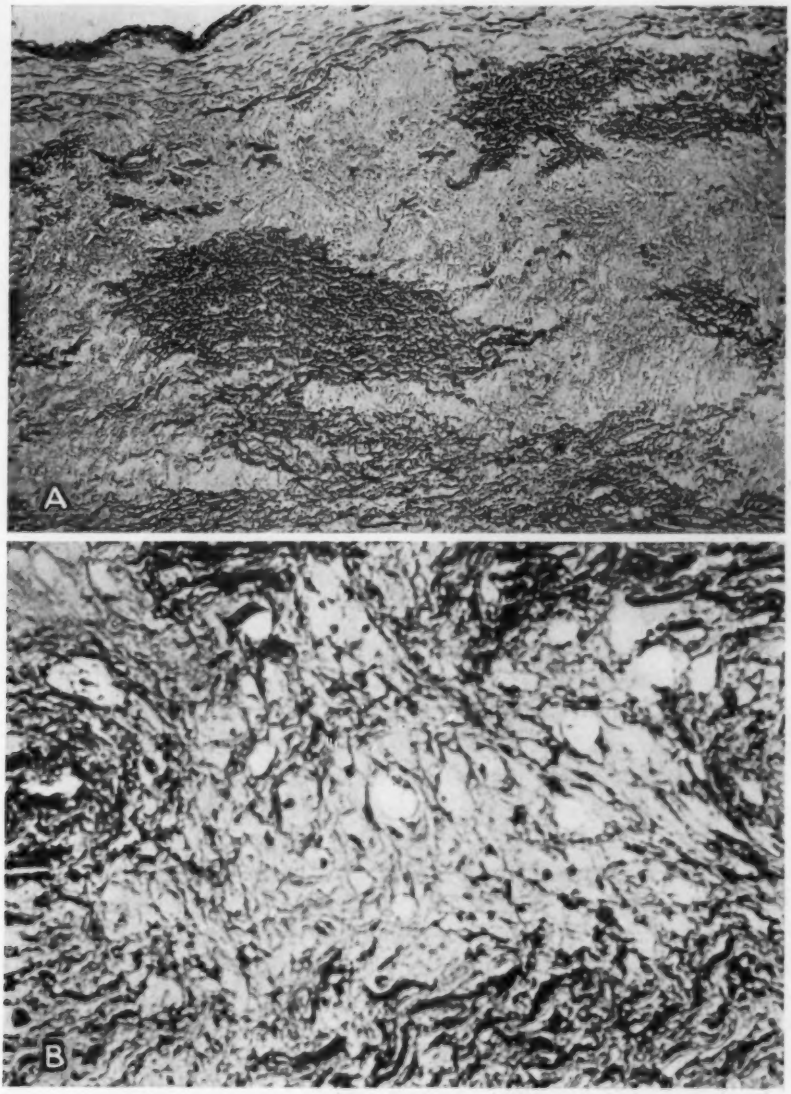

Fig. 4.—*A*, same lesion as in figure 3 *B*, illustrating the absence of elastic tissue; Weigert's stain for elastic tissue; low power magnification. *B*, nonvascularized scar filling an area of degeneration; phosphotungstic acid-hematoxylin stain. Note looseness of the stroma. Fibroblasts are scant.

(fig. 4 *B*). Though these scars were usually avascular, an occasional one contained wide endothelial-lined channels. Inflammatory reaction was completely absent from this type in every case.

No correlation could be established between intimal changes and the medial lesions. To be sure, some were subjacent to atherosclerotic plaques, both small and large, but these were the exceptions. It was impossible to discover adventitial thickening beneath the medial lesions as described by Gsell, except in the last case, and in that instance it was generalized rather than focal.

Changes in the vasa vasorum found in several cases were due to increase either of elastic or of collagenous tissue.

The cardiac findings in the series are as follows: The hearts of 9 patients were hypertrophied. Four of the patients from whom these hearts were removed had clinical records of hypertension. Fusion of the commissures of the aortic valve with thickening of the leaflets was noted in 5 hearts. One alone had demonstrable Aschoff bodies in the myocardium. One showed myocardial infarction.

The degree of coronary disease was insignificant except in 3 hearts. In case *7*, in addition to atherosclerosis narrowing the lumen there was a marked inflammatory reaction of undetermined nature. In the third there was severe atherosclerosis but no occlusion.

COMMENT

Attempts to ascribe medial degeneration as seen in these cases to artefact or to change secondary to trauma or to nutritional insufficiency incidental to dissection can be dismissed. In the first place, it was found in nondissected portions of the aorta; secondly, it occurred rarely in the descending portion, which was as frequently dissected as the ascending aorta, and, finally, medial degeneration as herein described has been seen in our laboratory in routine autopsy material. One case was reported [16] in which the changes were more marked than in any instance in the present series. In that case there was aneurysm formation, but the wall was not dissected and not ruptured.

The disease is a distinct pathologic entity, different from any of the better known forms of aortic disease, such as syphilis and rheumatic fever, since the inflammatory changes characteristic in the latter two diseases are absent. In the same way, it differs from other less common forms of aortitis, such as those due to pyogenic infection, tuberculosis and periarteritis nodosa. This lack of inflammatory reaction in medial degeneration cannot be ascribed to inability of the organism to react, for in every instance in which hemorrhage had taken place in the adventitia numerous polymorphonuclear leukocytes were found

16. Rottino, A.: Arch. Path. **27**:320, 1939.

locally. Further, in older cases fibroblastic reaction was rich and new vascular channels abundant. The same proliferative phenomenon was noted on the dissected surfaces of the media, where in some instances a new intima was in the process of formation, seen par excellence in case 12, an instance of an old, healed lesion, where the reformed intima was dense, rich in collagen and densely packed with elastic fibrillae.

The finding of medial degeneration exclusively in the ascending aorta and arch in 11 of the 12 cases emphasizes Gsell's notation that it is essentially a disease of this portion of the vessel. Its progression from simple muscle loss to eventual cyst formation was a relatively simple matter to trace in 6 cases—an experience similar to that of Gsell's. Its inception in preliminary mucoid degeneration in the sense of Erdheim, on the other hand, could not be established. To be sure, in 4 cases there was degeneration of media with unusual collections of mucoid—surrounding abnormally arranged muscle or filling large spaces. To trace this to a lesion beginning with an overabundance of mucoid in single interlamellar spaces, however, was impossible.

A word must be said concerning the ability of smooth muscle to regenerate, since this potentiality is questioned by many pathologists. It is impossible in the cases herein presented to state that the evidence for this is the demonstration of visible mitosis or amitosis. However, when one sees in an area an increase in muscle cells, not ascribable to crowding, one is driven to the conclusion that they must have regenerated, possibly from nonaffected peripheral cells. Further proof is that in large areas of degeneration, as evidenced by loss of elastic tissue, one still finds muscle cells in profusion. Unless they are regenerated, one is compelled to accept the theory that they represent the original muscle which escaped the effect of a noxa capable of destroying elastic tissue.

The causes are entirely unknown. Certain factors are apparently associated sufficiently often to suggest themselves as predisposing. Age is one, for no patient in the present group was younger than 43; one was 51, and the rest were above 55. However, since in the literature there are reports of cases in which the ages were 21,[10] 23,[5] 25,[4] 28[10] and 29,[17] it appears that the necessity of old age is not absolute. A second finding of importance is the presence of pathologic changes in the heart in some form. This was observed in 11 of 12 specimens—9 with hypertrophy and 5 with lesions of the aortic valve. One third of the patients (4 of 12) had had hypertension. Four others had hypertrophied hearts with no valvular defects to account for the enlargement. Unfortunately, their blood pressure had not been taken.

17. Narr, F. H., and Wells, A. H.: Am. Heart J. **8**:834, 1933.

The specific cause (or causes) remains problematic. Wiesel's [5] finding of medial degeneration in peripheral vessels of patients who died of acute infectious disease—sepsis or scarlet fever—has supplied one answer. Apparent support was given by Stoerk and Epstein,[18] who found the same change in the coronary vessels in fatal cases of grip. Gsell [4] suggested the importance of endogenous toxins. Three of his patients had renal insufficiency. Pappenheimer and Von Glahn [19] observed simple muscle loss in the aorta in several cases of rheumatic fever. They ascribed it to a nutritional disorder resulting from changes in and about the nutrient vessels. On the experimental side, degenerative lesions in the aorta have been reported in poisoning by nicotine, lead (Cellina [7]) and epinephrine (Lange [20]), in electrical and thermal stimulation of the wall (Erdheim [6b]); also, in consequence of feeding pulverized organs to rabbits (Steinbiss [21]). Erdheim, noting how unrelated the assumed causes were, came to the conclusion that all of them in some way were responsible for overproduction of epinephrine. In the proper patient this caused prolonged contraction of vasa vasorum and ischemic necrosis of the media. My material offers no help to any of the theories.

SUMMARY

Medial degeneration was studied in the aorta in 12 selected cases of dissecting aneurysm. The lesion was characterized by loss of muscle, elastic tissue and collagen, lack of inflammatory reaction and healing by loose scar formation and by regeneration of muscle and elastic tissue. Loss of muscle appears to be the initial lesion. The degeneration of the remaining medial elements follows.

Medial degeneration as described by Erdheim could not be established to be present in our material.

Medial degeneration is essentially a disease of the ascending aorta and arch.

The specific cause remains unknown. Possible predisposing causes are: old age, heart disease, hypertension.

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18. Stoerk, O., and Epstein, E.: Frankfurt. Ztschr. f. Path. **23**:163, 1920.
19. Pappenheimer, A. M., and Von Glahn, W. C.: J. M. Research **44**:489, 1924.
20. Lange, F.: Virchows Arch. f. path. Anat. **248**:463, 1924.
21. Steinbiss, W.: Virchows Arch. f. path. Anat. **212**:152, 1913.

TRICHINELLA SPIRALIS

I. INCIDENCE OF INFECTION IN MAN, DOGS AND CATS IN THE NEW ORLEANS AREA AS DETERMINED IN POSTMORTEM EXAMINATIONS

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The incidence of infection with Trichinella spiralis is higher in the United States than in any other country.[1] Practical methods for the reduction and control of the infection depend on knowledge of the incidence in the various hosts and the epidemiologic role these hosts play, in order that the most important transmission lines of this parasite may be interrupted.

Any mammal which eats trichinous muscle is apt to contract trichinella infection and on being eaten itself may act as a transmitter. Trichinellas occur not only in man but in the domestic and the wild hog, the captive and the wild bear, the mouse, the rat, the dog, the cat, the mongoose, the fox, the badger, the marten, the marmot, the polecat (skunk, fitchet), the raccoon, the ichneumon (Herpes ichneumon) and the hippopotamus. The transmission of T. spiralis from host to host is diagrammatically shown in figure 1. Only those animals are included which play a part in the epidemiology of trichinosis in the New Orleans area.

Man acquires trichinella infection by eating infected pork (exceptionally bear meat). Hogs acquire it by eating infected pork scraps or infected rats. Rats acquire it by eating other infected rats, infected pork scraps or infected carcasses of dogs or cats. Dogs become infected by eating infected pork scraps or infected rats. Cats obtain the infection by eating infected pork scraps, rats or mice, which in turn acquire it by eating infected pork scraps.

In order to ascertain the prevalence of T. spiralis in the New Orleans area, a survey of its incidence in man, hogs, rats, mice, dogs and cats has been conducted. This paper deals with the incidence in man, dogs and cats. The incidence in hogs, rats and mice has been studied in this laboratory by C. E. Peres, and his findings will be published later.

From the Parasitology Laboratory, Department of Tropical Medicine, Tulane University of Louisiana.

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1. Sawitz, W.: Pub. Health Rep. **53**:365, 1938.

In 1936 Hinman,[2] using the artificial digestion method, examined 2 square inches (12 sq. cm.) of each of 200 human diaphragms obtained at autopsies at the Charity Hospital in New Orleans and found 7 diaphragms infected with T. spiralis—an incidence of 3.5 per cent. This figure has been regarded as too low by McNaught and Anderson [3] and by Hall and Collins [4] on the ground that larger amounts of muscle, additional muscles or additional methods of examination might have yielded a higher incidence of infection.

METHODS

Human diaphragms and pectoral muscles were obtained at unselected routine necropsies in the Charity Hospital and the Touro Infirmary. Diaphragms of dogs

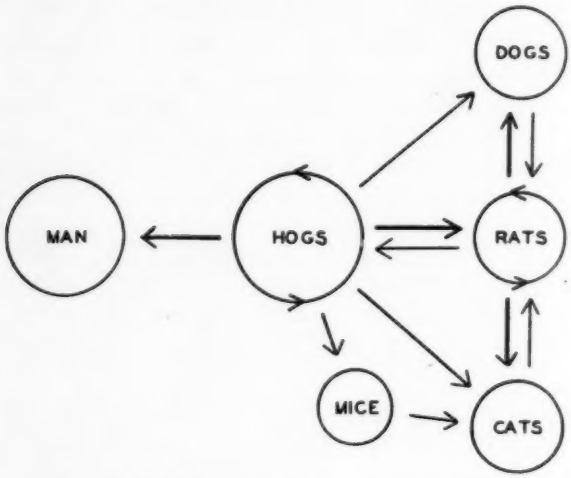

Fig. 1.—Transfer of trichinellas from host to host in the New Orleans area.

and cats were obtained from animals studied in various departments of Tulane University School of Medicine.

The muscles were separated from fat, and about half a gram of each muscle was pressed between two slides in a compressor similar to that used by the United States Bureau of Animal Industry. The piece of muscle was examined for larvae of T. spiralis under a dissecting binocular microscope, with a × 4 ocular and a × 18 objective.

In addition to the compressor method, the digestion method of collecting larvae of T. spiralis was employed—a method devised by Thornbury [5] in 1897 and first used to ascertain the incidence of trichinella infection in man by Queen,[6] in 1931.

2. Hinman, E. H.: New Orleans M. & S. J. **88**:445, 1936.
3. McNaught, J. B., and Anderson, E. V.: J. A. M. A. **107**:1446, 1936.
4. Hall, M. C., and Collins, B. J.: Pub. Health Rep. **52**:468, 1937.
5. Thornbury, F. J.: Univ. M. Mag. **10**:64, 1897.
6. Queen, F. B.: J. Parasitol. **18**:128, 1931.

The muscles were ground and weighed, and 100 cc. of artificial gastric juice was added to each 10 Gm. of ground tissue. The maximum amount of diaphragm used was 170 Gm; the smallest, 10 Gm; the average, 50.8 Gm. The maximum amount of pectoral muscle used was 150 Gm.; the smallest, 5 Gm.; the average, 34.6 Gm. The artificial gastric juice was a solution of 1 per cent pepsin and 0.5 per cent hydrochloric acid. Digestions were carried on for twelve to sixteen hours in an incubator at 37.5 C. (over night). The fluid was then strained through two layers of cheesecloth into a funnel 8 inches (20 cm.) in diameter, with a rubber tube and screw clamp attached to the funnel stem. After three hours 25 cc.

TABLE 1.—*Findings in Infected Human Diaphragms and Pectoral Muscles by Means of the Compressor and Digestion Methods*

	Diaphragms					Pectoral Muscles				
		Digestion Method					Digestion Method			
Case	Compressor Method	Amount of Tissue Examined, Gm.	Larvae	Calcified Cysts	Number per Gram	Compressor Method	Amount of Tissue Examined, Gm.	Larvae	Calcified Cysts	Number per Gram
1	0	50	0	0	0	+	10	1	0	0.1
2	0	30	2	0	0.07	0	15	1	0	0.07
3	0	20	0	1	0.05	0	10	0	0	0
4	0	50	0	3	0.06	0	20	0	0	0
5	0	80	2	0	0.01	0	10	0	0	0
6	0	50	0	21	0.4	0	10	0	6	0.6
7	0	50	0	31	0.6	0	15	0	6	0.4
8	0	50	6	0	0.12	0	15	2	0	0.13
9	0	40	0	38	0.95	0	15	0	7	0.47
10	0	60	0	3	0.05	0	10	0	1	0.1
11	0	50	2	0	0.04	0	70	0	0	0
12	0	110	8	1	0.07	0	55	3	1	0.07
13	0	30	17	1	0.6	0	35	7	3	0.29
14	0	40	0	6	0.15	0	10	0	0	0
15	0	90	0	9	0.1	0	10	0	0	0
16	0	27	0	0	0	0	60	2	0	0.03
17	0	60	0	2	0.03	0	50	0	0	0
18	0	60	2	2	0.07	0	60	0	0	0
19	0	35	0	10	0.28	0	30	0	1	0.03
20	0	60	0	25	0.42	0	60	0	0	0
21	0	25	0	0	0	0	35	1	0	0.29
22	0	25	0	9	0.36	0	45	0	3	0.06
23	0	85	0	13	0.15	0	30	0	0	0
24	+	90	497	0	5.52	Not examined				

of the fluid was drawn off into a Petri dish which had been ruled in squares. Each square had been numbered by means of a diamond pencil in order to facilitate counting. The fluid in the Petri dish was examined with a dissecting binocular microscope, using a × 4 ocular and a × 18 objective. Trichinellas found were differentiated as living larvae or calcified cysts, and the number of each was counted. The examination was repeated with more fluid until two successive samples were negative.

INCIDENCE IN MAN

Examinations were made of tissues obtained at 400 unselected routine autopsies, including 200 previously reported.[7] Larvae of T. spiralis were found in 24 cases—an incidence of 6 per cent.

7. Sawitz, W.: Am. J. Pub. Health **27**:1023, 1937.

The quantitative data on the findings in the diaphragms and pectoral muscles by the compressor and digestion methods are presented in table 1.

Of the 24 instances of trichinella infection, 2 were found by the compressor method (cases 1 and 24), while all were found by the digestion method. In view of the fact that only half a gram of muscle was examined by the compressor method, it was to be expected that the cases detected by this method would be those in which at least 1 larva was present in half a gram of tissue. Cases with less than 1 larva in half a gram of tissue would be expected to be discovered according to the chances of probability. Only 1 of the 24 cases (case 24) showed more than 1 larva in half a gram of tissue by the digestion method, and this case was found by the compressor method. The case in which the digestion method revealed 0.1 larva in 1 Gm. (case 1) was probably found by chance. In the digestion method a much larger amount—on the average 50.8 Gm. of diaphragm and 34.6 Gm. of pectoral muscle—was used, and the larvae present were collected in the sediment. This technic serves as a concentration method.

Of the 23 cases in which both the diaphragm and the pectoral muscle were available, the parasites were shown in the diaphragm in 20—an incidence of 87 per cent. In 13 cases the parasites were shown in the pectoral muscle—an incidence of 56.5 per cent. In other words, if the diaphragm alone had been examined, 13 per cent of the cases of infection would have been missed, and 43.5 per cent if only the pectoral muscle had been examined. According to Thornbury,[5] the diaphragm is considered the best material in which to discover the larvae of T. spiralis. He found them in the diaphragms of 76.6 per cent of 1,043 trichinous swine, while 23.4 per cent of the infected swine had the larvae only in loin or neck muscles or both. No such studies seem to have been made in man. The comparative figures in the present study indicate that the diaphragm is a better site for discovering the larvae than is the pectoral muscle and that the distribution in man may be similar to that in swine. The figures 76.6 per cent for hog diaphragms and 87 per cent for human diaphragms might have been still closer if additional muscles had been examined, since then the figure for the total incidence might have been greater, and thus the percental incidence in the diaphragms lower.

To facilitate comparison of the quantitative findings in diaphragms and pectoral muscles, the cases are arranged in table 2 according to the intensity of infection.

The average number of trichinellas found per gram of diaphragm in the 10 cases in which both the diaphragm and the pectoral muscle were infected was 0.35, whereas the average number in the pectoral muscle was 0.22 per gram. This indicates that the diaphragm is not

only qualitatively but also quantitatively the better material in which to search for these parasites. The value of the surgical removal of a piece of pectoral muscle for diagnostic purposes is not diminished by these results, since the biopsy method is employed in cases of clinical trichinosis, in which a heavy general infection and thus infiltration of the pectoral muscles may be expected.

Hall and Collins [4] advanced the theory that the rapidity with which the larvae die and calcify is proportional to the intensity of the infection. They found only living larvae in the majority of infections with less

TABLE 2.—*Order of Cases with Regard to Increasing Intensity of Infection in the Diaphragmatic Tissue*

Case	Age of Patient	Larvae Found per Gram in Diaphragm	Larvae Found per Gram in Pectoral Muscle	Living (L) or Calcified (C)
1	43	0.00	0.1	L
16	44	0.00	0.03	L
21	45	0.00	0.29	L
5	40	0.01	0	L
17	50-60	0.03	0	C
11	60	0.04	0	L
3	61	0.05	0	C
10	48	0.05	0.1	C
4	65	0.06	0	C
2	29	0.07	0.07	L
12	32	0.07	0.07	L, C
18	49	0.07	0	L, C
15	51	0.1	0	C
8	60	0.12	0.13	L
14	57	0.15	0	C
23	76	0.15	0	C
19	59	0.28	0.03	C
22	73	0.36	0.06	C
6	70	0.4	0.6	C
20	73	0.42	0	C
7	56	0.6	0.4	C
13	60	0.6	0.29	L, C
9	36	0.95	0.47	C
24	48	5.52	Not examined	L

than 1 larva per gram; in infections with 1 to 10 larvae per gram, some of the larvae were living and some were dead; in cases with more than 10 larvae per gram, mixed infections or only calcified cysts were found. In 23 of the cases there was less than 1 larva per gram. In 7 of these only living larvae were found, in 3 a mixed infection and in 13 only calcified cysts. In the single case in which more than 1 larva per gram occurred, only living ones were observed. However, on dividing the cases into two groups, one the cases with less than 0.1 trichinella per gram and the other those with more, one notes in the first group 12 cases, 6 (50 per cent) of which showed only living larvae, 2 (16.6 per cent) a mixed infection and 4 (33.3 per cent) calcified cysts. Of the 12 cases of the second group, 2 (16.6 per cent) showed only living larvae, 1 (8.3 per cent) a mixed infection and 9

(75 per cent) calcified cysts. These figures seem to support the theory of Hall and Collins.

The age, sex, color and nativity of the patients are recorded in table 3.

The incidence of infection in the first 100 cases examined was 4 per cent, in the second 6 per cent, in the third 7 per cent and in the fourth 7 per cent. A variation of 4 to 7 per cent in 100 cases is in the same range as that found by Nolan and Bozicevich [8] in their study of 1,000 diaphragms, their lowest incidence being 12 per cent in one series of 100 cases, their highest 24 per cent. In addition, the

TABLE 3.—Age, Sex, Color, Nativity and Occupation of the Persons Found Infected

Person	Age	Sex	Color*	State of Birth	Occupation
1	43	M	W	Texas	Bartender
2	29	F	N	La.	Housewife
3	61	M	W	La.	Horse trainer
4	65	F	W	La.	Housewife
5	40	M	W	La.	None
6	70	M	N	?	None
7	56	F	W	La.	Housewife
8	60	M	W	La.	Laborer
9	36	M	N	La.	Laborer
10	48	M	N	La.	Laborer
11	60	F	N	La.	Housewife
12	32	M	N	La.	Laborer
13	60	M	N	N. C.	None
14	57	F	W	La.	Seamstress
15	51	F	N	La.	Housewife
16	44	F	N	La.	Cook
17	50-60	M	N	La.	Laborer
18	49	F	N	La.	None
19	59	M	W	La.	?
20	73	M	N	Texas	None
21	45	F	N	La.	Truck driver
22	73	F	N	La.	Farmer
23	76	M	W	La.	None
24	48	M	N	La.	Laborer

* W indicates white; N, Negro.

incidence will vary, according to the chances of probability, with age, sex, race, nationality and economic status, as demonstrated by Hall and Collins.[9]

The mean average age of the first 100 patients whose tissues were examined post mortem was 44.52 years, of the second 100 patients 44.9 years, of the third 100 patients 46.35 and of the fourth 100 patients 44.76. In addition, 13 patients included in the first group were of a higher economic status than the others. These factors may account for the lower incidence in the first 100 patients.

In the 24 patients found infected, no clinical symptoms of light or chronic trichinella infection had been noted. This is in accordance

8. Nolan, M. O., and Bozicevich, J.: Pub. Health Rep. **53**:652, 1938.
9. Hall, M. C., and Collins, B. J.: Pub. Health Rep. **52**:512, 1937; footnote 4.

with the findings in previous surveys in other areas. The highest eosinophil count in the 24 cases of infection was 1 per cent. However, in only 4 of the 24 cases were blood counts available. The findings in these 4 cases are given in table 4.

The small number of cases in which blood counts were available does not warrant the conclusion that small numbers of trichinellas, even living ones, do not stimulate or sustain eosinophilia. The time that elapses between the exposure to infection and the examination of the blood plays an important part, since the number of eosinophils

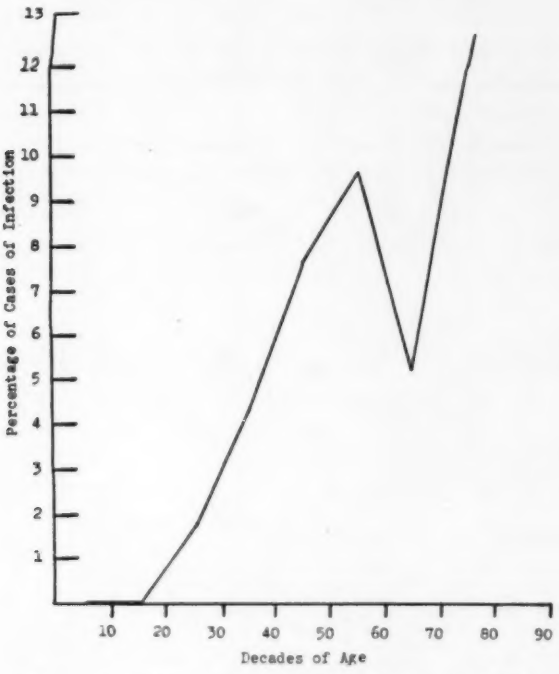

Fig. 2.—Percental incidence of trichinella infection by decades of age.

decreases in the course of time after it has reached a maximum in the acute stage. In a case of clinical trichinosis which was followed up, the percentage of eosinophils was 36 per cent four weeks after exposure, 10 per cent after one year and 2 per cent after two years. This suggests that in these 4 cases infection occurred at least two years before death.

The distribution of the cases by decades of age is shown in table 5.

Figure 2 shows the curve of the percental distribution of the cases of infection by decades of age. It shows an increasing incidence of trichinella infection with increasing age. Since the chances of becoming

infected increase with age, the rising curve is understandable. In the group who were examined in the first decade are included 2 stillborn infants and 3 babies under 1 year of age, all 5 found uninfected. The negative findings in the first and second decades are in agreement with the report of McNaught and Anderson,[3] who did not find infection in

TABLE 4.—*Eosinophil Counts in Four Cases*

Case	Total White Cell Count	Eosinophils, Per Cent	Larvae of Trichinella Found per Gram
2	10,500	0	0.07, living
20	7,000	0	0.42, calcified
21	11,400	0	0.29, living
22	10,400	1	0.36, calcified

TABLE 5.—*Distribution of the Cases by Decades of Age*

Decades of Age	Cases in Which Tissues Were Examined	Cases in Which Tissues Were Found Infected		
		Number	Percentage	
0-10	17	0	0	
11-20	18	0	0	
21-30	54	1	1.85	4.27
31-40	69	3	4.34	
41-50	76	6	7.89	
51-60	82	8	9.76	
61-70	58	3	5.17	8.48
71-80	24	3	12.5	
81-90	1	0	0	
Unknown	1	0	0	
	400	24	6	

TABLE 6.—*Distribution of Trichinella Infection According to Sex and Color*

Race	Males Examined	Males Infected		Females Examined	Females Infected		Total		
		Number	Percentage		Number	Percentage	Number Examined	Number Infected	Percentage Infected
White	105	6	5.71	59	3	5.08	164	9	5.43
Negro	131	8	6.10	105	7	6.66	236	15	6.36
	236	14	5.93	164	10	6.09	400	24	6

a single person under 25 years of age. No explanation can be offered for the drop in the seventh decade. A similar drop was found by Hall and Collins [4] in the eighth decade.

The distribution of trichinella infection according to sex and color is shown in table 6.

The incidence in males (5.93 per cent) and that in females (6.09 per cent) are close. This is in agreement with the reports of McNaught and Anderson [3] and Hall and Collins,[9] who did not find any essential

difference in the incidence in these two groups. Analyzing these figures and considering the incidence for white males, white females, Negro males and Negro females separately, one finds the highest incidence in Negro females and the lowest in white females. Hall and Collins [9] also found the highest incidence in Negro females; the lowest incidence, however, they found in Negro males. They explained the sex difference (19.6 per cent in Negro females and 4.2 per cent in Negro males) by the fact that Negro females working as cooks are more exposed to infection through their tasting of raw and undercooked pork and pork products while engaged in their tasks. In the present series the number of those listed as cooks or servants is only 3. While Negro people may be less "trichinella conscious," they usually prepare their meat in a rather overdone manner, whereas white women, although they know more about the danger, like their pork rather underdone. Since in this series no sea-going persons are listed, a group in which Hall and Collins showed the highest incidence among white persons, it is understandable that the high incidence found by these observers in white males is not matched in the present series. The differences in the groups based on sex and color are not enough to be significant.

Almost all of the 400 persons whose diaphragms and pectoral muscles were examined belonged to the group of low economic status. Hall and Collins [9] found an incidence of 9.6 per cent in persons of high economic status and 14.6 per cent in persons of low economic status. They explain the difference by the food habits in these groups. If the ratio of incidence in their two groups is applicable to the incidence in the population of the New Orleans area, the 6 per cent incidence found in persons of low economic status corresponds to a 3.9 per cent incidence in the group of high economic status. The 13 persons of high economic status examined in the present series were not found infected.

Infection was found in 20 of 339 persons listed as natives of Louisiana, in 2 of 3 from Texas and in 1 of 4 whose nativity could not be ascertained. None of the 3 persons from Germany, 3 from Italy, 2 from France, 1 from Ireland and 1 from Greece was found infected. Since it is not known how long they lived in their native country and in this area, no significance can be attributed to this relationship of trichinella infection and nativity.

INCIDENCE IN DOGS

The diaphragms of 300 dogs were examined by the digestion method. Larvae of T. spiralis were recovered in 4—an incidence of 1.3 per cent. All infections were light; only living larvae were found —no calcified cysts.

Brumpt [10] mentioned that in 1913 Hjortlund in Denmark found trichinella infection in 0.4 per cent of dogs. According to von Ostertag,[11] the incidence among dogs in Germany examined in 1904 to 1934 was 0.2 per cent. Yugawa [12] in Manchuria found 14 trichinous dogs among 179 street dogs of Liaoyang and Mukden in 1934—an incidence of 7.97 per cent. No survey of dogs for trichinellas seems to have been made previously in the United States.

INCIDENCE IN CATS

The diaphragms of 90 cats were examined by the digestion method. Nine cats were found infected—an incidence of 10 per cent. Five of these cats were heavily infected, as shown by the number of recovered trichinellas. Only living larvae were found—no calcified cysts.

In Denmark Hjortlund [13] found an incidence of 2 per cent in cats; in Rumania Cernaianu [13] found an incidence of 8 per cent. In 1937 Ch'in [14] found trichinellas in the tongue of a cat in Mukden. In the United States Riley [15] examined 25 cats in Saint Paul, Minn., and found 3 infected—an incidence of 12 per cent. On another occasion he found 1 cat infected among 5 examined, i. e., an incidence of 20 per cent. Riley concluded that cats play a considerable part in the perpetuation of endemics of T. spiralis. A survey of cats in order to ascertain the incidence of T. spiralis in them and the possible importance of cats in the epidemiology of T. spiralis does not seem to have been made. In passing, it is of interest to note that the first infection of lower animals with T. spiralis was found in cats by Herbst,[16] in 1845.

COMMENT

Since the majority of the persons from whom the examined tissues came belonged to the group of low economic status, this series does not represent a cross section of the population. Following Hall's [9] ratio between the groups of low and high economic status, the 6 per cent incidence in this group of low economic status would correspond to a 3.9 per cent incidence in the group of high economic status; the incidence in the entire population could be computed as being between 4 and 6 per cent. Although Hinman [2] examined approximately the same group of the population, his positive findings indicated an incidence

10. Brumpt, E.: Précis de parasitologie, Paris, Masson & Cie, 1936, p. 1047.

11. von Ostertag, R.: Leitfaden für Trichinenschauer, ed. 6, Berlin, Verlagsbuchhandlung von Richard Schoetz, 1935, p. 61.

12. Yugawa, T.: J. Orient. Med. **21**:88, 1934.

13. Cited by Brumpt.[10]

14. Ch'in, Y. T.: Chinese M. J. **51**:500, 1937.

15. Riley, H. A.: Ann. de parasitol. **6**:477, 1928.

16. Herbst, cited by Stäubli, C.: Trichinosis, Wiesbaden, J. F. Bergmann, 1909.

of 3.5 per cent as compared with the 6 per cent which is reported here. If diaphragms alone had been examined, as in Hinman's series, the incidence reported here would have been 5.25 per cent. The difference between 3.5 and 5.25 is probably due to the larger amounts of muscle examined in the present study, since Hinman used only approximately 10 Gm. of diaphragm. He should, therefore, have found only those cases in which there was at least 1 larva in 10 Gm. or 0.1 larva per gram of tissue. Applying this method to the present series, I find the incidence to be only 4.25 per cent, a figure not far from the 3.5 per cent reported by Hinman. Thus, the data of the present investigation support Hinman's conclusion that the incidence of trichinella infection in the New Orleans area is the lowest in the United States so far as surveys made up to the present show.[1]

The examination of dogs and especially that of cats showed that T. spiralis is present in this area. While man may acquire the infection away from his home area, cats, especially, do not migrate far. The incidence in cats, therefore, is considered a true index of endemicity of trichinella infection and an indication of the possibility of human infection.

The conclusions to be drawn from these findings will be discussed in a subsequent paper on the epidemiologic aspects of trichinella infection, after the survey of the various hosts in the New Orleans area is completed.

SUMMARY

Examination of human diaphragms and pectoral muscles obtained in four hundred routine unselected necropsies disclosed 24 cases of infection with T. spiralis in the New Orleans area—an incidence of 6 per cent. The compressor method detected 2 cases; the digestion method, 24. Of the 23 cases in which both the diaphragm and the pectoral muscle were available, the diaphragm was found infected in 20 cases, or 87 per cent, and the pectoral muscle in 13 cases, or 56.5 per cent. Surveys in which diaphragms only are examined would thus miss 13 per cent of the cases. The average number of larvae of T. spiralis found in the diaphragm was 0.35 per gram; the average number in the pectoral muscle, 0.22 per gram. The diaphragm is, therefore, not only qualitatively but also quantitatively the better tissue for examination. No history of clinical symptoms of trichinosis was found in any of the 24 cases. With increasing age the incidence of trichinella infection increased. The highest incidence was found in Negro females (6.66 per cent); the lowest, in white females (5.8 per cent).

The incidence of trichinella infections in 300 dogs in the New Orleans area was found to be 1.3 per cent, the incidence in 90 cats was found to be 10 per cent. The incidence in cats is considered to serve as an indicator of the endemicity of trichinella infection in an area.

SCLEROSIS OF THE SUPERIOR VENA CAVA IN CHRONIC CONGESTIVE HEART FAILURE

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It has been generally accepted [1] that persistent local increase of intra-arterial pressure is a prime cause of arteriosclerosis in both the greater and the lesser circulation. Sclerosis of the veins in the course of increased intravenous pressure of long duration has been less frequently described, largely because chronically increased intravenous pressure is relatively uncommon.

While direct measurements of the pressure in the human superior and inferior venae cavae are not available, it is well established that in patients suffering from chronic congestive heart failure the pressure in the peripheral veins may be greatly increased. Since the pressure in these veins is transmitted directly from the heart, the pressure in the venae cavae must also be elevated. One of us (H. G.)[2] demonstrated sclerosis of the inferior vena cava and of the hepatic veins in chronic congestive heart failure. The purpose of this study was to determine whether similar changes occur in the superior vena cava.

REVIEW OF THE LITERATURE

Moschcowitz [1] is of the belief that increased tension is the sole cause of both arteriosclerosis and phlebosclerosis. Ljungdahl [3] as well as Miller [4] reported the frequent occurrence of pulmonary arteriosclerosis associated with hypertension of the lesser circulation occurring in mitral stenosis. The former noted that in many of the cases the pulmonary veins also showed sclerosis. He observed greater sclerosis in the arteries than in the veins and attributed the greater changes to the higher pres-

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1. Moschcowitz, E.: Am. J. M. Sc. **178**:244, 1929; Phlebosclerosis of the Hepatic Veins, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 857.

2. Gross, H.: Arch. Path. **23**:457, 1937.

3. Ljungdahl, M.: Untersuchungen über die Arteriosklerose des kleinen Kreislaufs, Wiesbaden, J. F. Bergmann, 1915.

4. Miller, H. R.: M. Clin. North America **9**:673, 1925.

sure within the arteries as well as to nutritional disturbances. He called attention to the similarity of phlebosclerosis to arteriosclerosis and noted the relationship between the degree of increased tension within the lumen and the degree of dilatation of a vessel. While Kaya [5] noted the frequent association of phlebosclerosis and chronic stasis, he doubted that congestive heart failure alone could cause phlebosclerosis in young persons. Schilling [6] also observed phlebosclerosis at sites of increased pressure and reported that in a series of 75 cases phlebosclerosis was due to congestion in 33. Waaler [7] observed hyaline plaques in the superior vena cava and in the right auricle. He regarded them as representing either the final and healed stage of lesions of acute rheumatic fever or sclerosis from long-standing heart disease. Allen and Page,[8] however, denied that sclerosis of the inferior vena cava occurred secondary to chronic congestive heart failure.

Sack [9] was of the belief that phlebosclerosis is part of a generalized vascular disease. Schilling [6] and Simmonds,[10] however, insisted on the independence of phlebosclerosis from arteriosclerosis. Hauswirth and Eisenberg [11] regarded phlebosclerosis as a disseminated process found frequently in association with peptic ulcers.

In portal cirrhosis, in which the dynamic factor of increased intravenous pressure is present, Simmonds [10] recorded sclerosis of the portal vein. Lossen [12] reported sclerosis of the portal, splenic, mesenteric and coronary veins in portal cirrhosis with hepatosplenomegaly. McIndoe [13] demonstrated sclerosis of both the portal system and the hepatic veins in portal cirrhosis.

Carrel [14] found scars in arteriovenous anastomoses, especially at points where the caliber of a vessel changed. The vein reacted to the arterial pressure by increase in thickness and strength of its wall, observed histologically to be the result of hypertrophy. Reid [15] was of the opinion that the altered intravascular pressure was responsible for the final atrophy of the artery and hypertrophy of the vein. Callander [16] noted increasing dilatation of the veins in arteriovenous fistulas, due

5. Kaya, R.: Virchows Arch. f. path. Anat. **189**:466, 1907.
6. Schilling, W.: Virchows Arch. f. path. Anat. **262**:658, 1926.
7. Waaler, E.: Am. J. Path. **13**:855, 1937.
8. Allen, E. V., and Page, I. H.: Deutsches Arch. f. klin. Med. **168**:193, 1930.
9. Sack, G.: Virchows Arch. f. path. Anat. **112**:403, 1888.
10. Simmonds, M.: Virchows Arch. f. path. Anat. **207**:360, 1912.
11. Hauswirth, L., and Eisenberg, A.: Arch. Path. **11**:858, 1931.
12. Lossen, J.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **13**:752, 1904.
13. McIndoe, A. H.: Arch. Path. **5**:23, 1928.
14. Carrel, A.: Technique and Remote Results of Vascular Anastomoses, in Studies from the Rockefeller Institute for Medical Research, 1912, vol. 15, no. 27.
15. Reid, M. R.: Am. J. Surg. **14**:17, 1931.
16. Callander, C. L.: Johns Hopkins Hosp. Rep. **19**:259, 1920.

in his opinion to the rise of venous pressure from passage of arterial blood through the sac. Kaufmann [17] described sclerosis of the walls of varicose veins. Benda [18] reported similar changes and observed intimal thickening, deposition of fibrous tissue, muscular atrophy, new formation of elastic tissue and connective tissue infiltration within and between the muscle bundles of the media of veins.

ANALYSIS OF MATERIAL

Before proceeding with the presentation of our findings it is advisable to discuss briefly the structure of the normal superior vena cava. As Franklin [19] ably pointed out in his excellent monograph on the veins, no true understanding of the histology of these vessels can be obtained without a consideration of their function and location.

The superior vena cava, owing to its large blood flow, its low venous pressure and the support afforded by the mediastinal structures, is a large thin-walled vein. Its endothelial lining merges imperceptibly with that of the right auricle. The intima is narrow and rests on a narrow network of interlacing elastic fibers. Collagen occurs in spirals in the superior vena cava and in vessels that vary in length. The well developed circular muscle in the media and adventitia of the inferior vena cava and in the veins of the lower extremities as compared with the thinner-walled veins of the upper parts of the body, which are poor in muscle fibers and collagen, is definitely related to greater internal pressure in the former vessels. The function of the circular elastic fibers is to accommodate sudden increases in content. The longitudinal elastic fibers prevent collapse of vessels of low internal pressure. Sparsely scattered individual smooth muscle fibers are found in this layer. The rather wide and loosely constructed adventitial layer surrounds the media, and in the outer portions of this layer are seen bundles of cardiac muscle. These fibers, which no doubt give support to the vessel wall, ascend in a spiral direction for variable distances along the vein.

The superior venae cavae from 21 persons with chronic congestive heart failure were examined post mortem. As control material the venae cavae from patients who during life and at necropsy showed no evidence of cardiac insufficiency or cardiac disease were used.

Tissue was taken at a point within 3 cm. of the junction of the superior vena cava with the right auricle. The gross appearance of the wall was noted, and

17. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, Berlin, W. de Gruyter & Co., 1922.

18. Benda, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2.

19. Franklin, K. J.: A Monograph on Veins, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

the material was fixed according to standard technics. Histologic sections 6 microns thick were stained with hematoxylin and eosin and with Verhoeff's elastic tissue stain and Van Gieson's stain. The sections were then examined without knowledge of the clinical diagnoses, in order to remove any prejudicial factor.

Of the 21 patients with chronic congestive heart failure, 14 were males and 7 were females; the ages ranged from 47 to 70 years. No attempt was made to select material from those in whom congestive heart failure was due to any particular etiologic agent. The causes of congestive heart failure in these patients were hypertensive cardiovascular disease in 15, arteriosclerotic cardiovascular disease in 2, rheumatic cardiovascular disease in 2 and cor pulmonale cardiovascular disease in 2. The duration and severity of the congestive heart failure in 21 of these patients are given in the table.

The superior venae cavae from 2 persons with hypertensive cardiovascular disease and 1 person with subacute bacterial endocarditis were examined also. Of the former one died following coronary thrombosis; the other died of a cerebral insult. None of these suffered from congestive heart failure.

The venae cavae from 8 persons not dying of cardiac diseases were also examined. The diagnoses in this group were chronic pulmonary tuberculosis in 5, status asthmaticus in 1, generalized sarcomatosis in 1 and Kaposi cell sarcoma in 1.

Duration and Severity of Congestive Heart Failure in Twenty-One Cases

Duration, Yr.	Cases	Cases of Given Type: Moderately Severe	Cases of Given Type: Severe	Duration, Yr.	Cases	Cases of Given Type: Moderately Severe	Cases of Given Type: Severe
1	3	1	2	5-10	4	0	4
1-2	4	2	2	10-16	2	1	1
2-5	8	6	2				

DATA

Superior Venae Cavae from Group with Chronic Congestive Heart Failure.—Macroscopic changes were found in only 2 of the 21 superior venae cavae examined. One of these was from a person with moderate congestive failure of eight months' duration; the other was from a person with multiple myocardial infarction and severe failure of seven years' duration. The alterations in each vein consisted of slightly raised yellowish plaques, varying in size from 0.5 to 2 cm. in diameter. Microscopically, these areas were composed of definite accumulations of loose connective tissue separated by rather wide tissue spaces, which in the latter vein were infiltrated by numerous small round cells.

Microscopic intimal alterations were observed in 18 of the 21 veins. In 4 there was slight thickening of this layer, while in the remaining 14 moderate to marked thickening was present. The thickening was largely the result of an increase in collagenous connective tissue. In 6 veins smooth muscle elements were also found in the thickened intima. In addition to the plaques described, a microscopic plaque composed of an acellular homogeneous hyaline substance was found in a vein

from a patient with hypertensive cardiovascular disease and diabetes who had suffered from progressively severe congestive heart failure for two years. Finally, a small connective tissue scar was found in a vein from a patient who had chronic rheumatic heart disease with severe congestive failure of four years' duration. The scar was infiltrated with small round cells, but no Aschoff bodies were found. Whether this scar represented the terminal healed phase of an Aschoff body or was

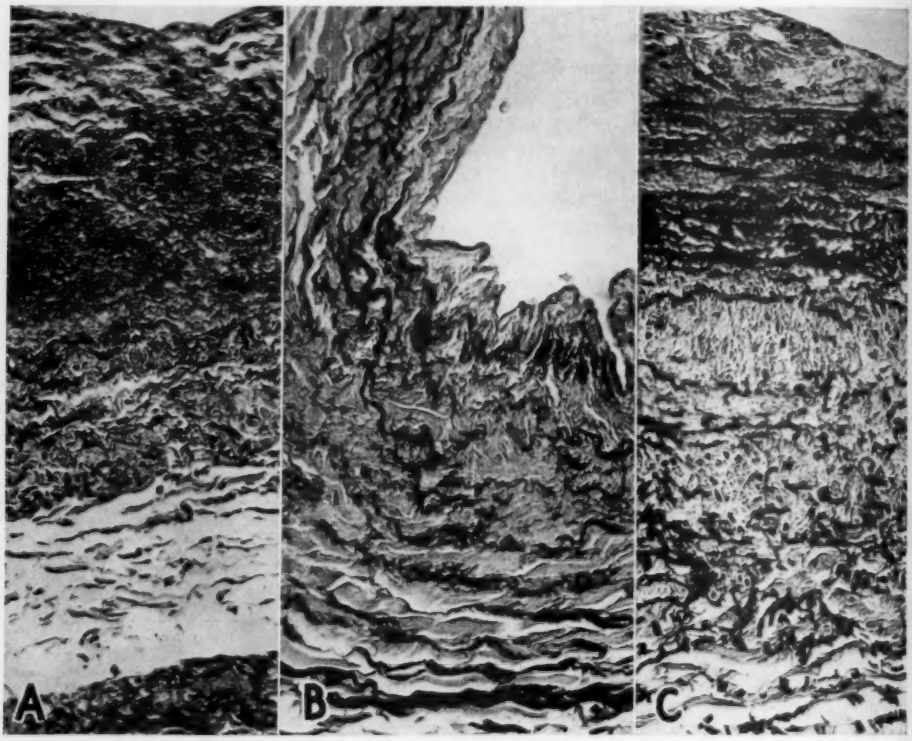

Fig. 1.—*A*, marked intimal and medial hypertrophy in the superior vena cava of a man of 64 years with hypertensive heart disease and moderate congestive heart failure of eight months' duration; × 100. *B*, thickening of the intima, splitting and reduplication of the elastica and hypertrophy of the media due to dense deposits of collagen and hyperplasia of the smooth muscle cells in the superior vena cava of a woman of 73 years with hypertensive heart disease and known congestive heart failure of three months' duration; × 100. *C*, raised intimal plaque with round cell infiltration and medial hypertrophy in the superior vena cava of a man of 57 years with severe hypertensive heart failure of seven years' duration; cardiac muscle is present in the adventitia; × 200.

a sclerotic patch due to chronic congestive heart failure cannot be stated. Alterations in the internal elastic layer were observed in 10 veins. These changes consisted chiefly of thickening, splitting and reduplication of

the elastic fibers, so that in some cases as many as three separate and distinct layers could be discerned.

Hypertrophy of the media due to the presence of numerous smooth muscle cells, hypertrophy of the smooth muscle cells and hypertrophy of the collagenous fibers was the most constant observation in the superior venae cavae in cases of congestive heart failure. Thickening

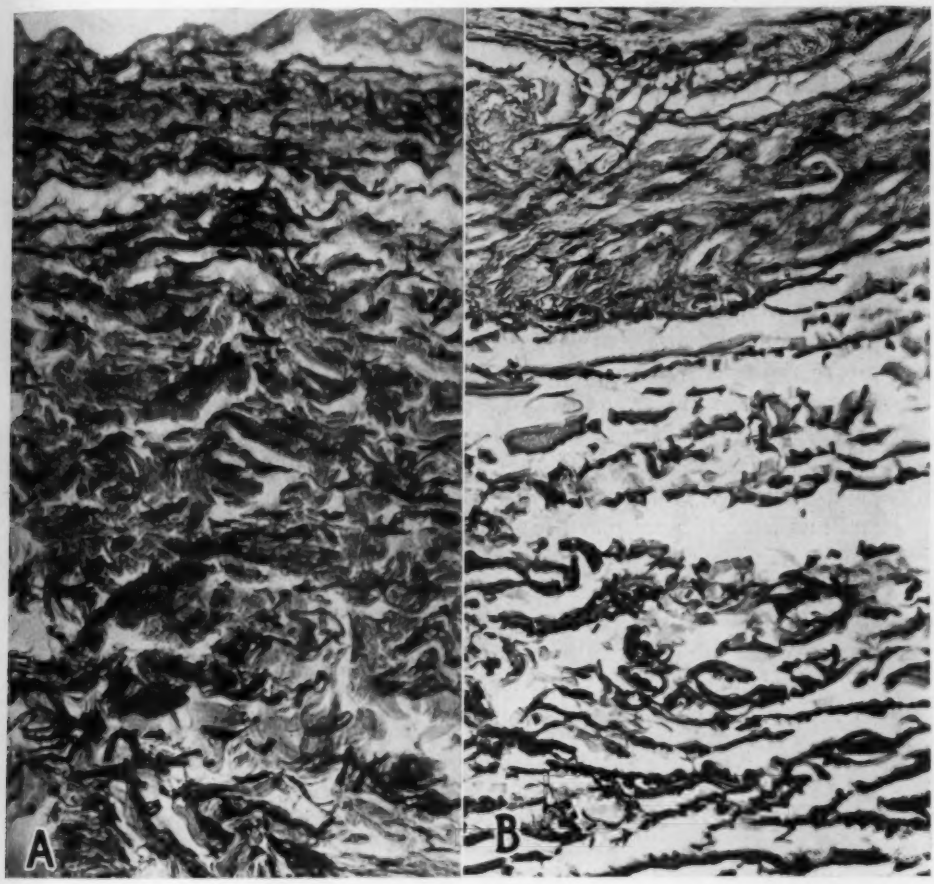

Fig. 2.—*A*, medial hypertrophy, with a large amount of collagen and large numbers of fragmented smooth muscle cells, and ingrowth of elastica in the superior vena cava of a man of 51 years with severe hypertensive heart failure of six years' duration; × 240. *B*, marked medial hypertrophy due to marked hyperplasia of smooth muscle cells and collagen in the superior vena cava of a man 61 years old with diabetes and hypertension and progressively severe congestive heart failure of two years' duration; × 200.

of the media was marked in 11 instances, moderate in 6 and absent in the remaining 4. In some cases collagenous fibers were arranged in an irregularly fragmented, bizarre fashion suggesting old scars. Smooth

muscle fibers were found in the media of 19 of the sections studied. In 12, the muscle cells were found in abundance, while in the other 7 they were scattered and few.

In 17 of the 21 veins the increase in the muscle fibers was coincident with hypertrophy of the media. Although in the remaining 4 veins there was no increase in thickness of the media, other significant changes were present. Marked intimal changes were found in 3, and scattered or numerous smooth muscle cells were present in 2 others. Combined medial and intimal changes occurred in 14; combined medial and elastica alterations occurred in 8. Intimal thickening and elastica changes were combined in 9 veins and in only 7 were alterations in all three layers seen. It is noteworthy that no vein in this group demonstrated changes in less than two layers.

Superior Venae Cavae from Group Not Having Congestive Heart Failure.—Macroscopic changes were found in none. Slight thickening of the intima was noted in the superior venae cavae from a patient with hypertension, a patient with rheumatic heart disease and subacute bacterial endocarditis and a patient with pulmonary tuberculosis and hypertrophy of the right ventricle. Moderate thickening of the intima occurred in but one vein in this group, that of a patient with hypertension. Splitting or reduplication of the elastica was found in the veins of 2 patients with pulmonary tuberculosis, 1 of whom had hypertrophy of the right ventricle. The media was moderately hypertrophied in 2 veins and markedly hypertrophied in 2 others. The latter were, respectively, from a patient with hypertension who died in status asthmaticus of acute failure of the right side of the heart and from a patient with subacute bacterial endocarditis engrafted on rheumatic mitral disease who at necropsy was observed to have chronic passive congestion of the liver and spleen. The vein of the latter showed also a round cell infiltration, so that it is possible that the findings represent the end stage of an Aschoff body in a vein.

Muscle fibers were observed in the media in 5 veins. In 3 veins (1 from a patient with pulmonary tuberculosis and hypertrophy and dilatation of the right side of the heart and 2 from patients with hypertension) the muscle cells were few. A large number of muscle cells was present in the media of a vein from a rheumatic patient with chronic passive congestion of the liver and spleen and in that of a tuberculous patient; both patients showed hypertrophy and dilatation of the right side of the heart.

In summary, in this group, involvement of the superior vena cava was minimal, none showing significant hypertrophy of the intima or media. In no single instance of the 11 were changes found in all the layers of the vein. Furthermore, in those in which definite hypertrophy

or sclerosis of the superior vena cava was noted there was increased tension in the right side of the heart due either to pulmonary tuberculosis and fibrosis, hypertension or mitral stenosis. The alterations were less marked and occurred as isolated phenomena in some of the superior venae cavae of the group not in congestive failure. It is striking that even in those instances in which there was increased tension in the right side of the heart the degree of hypertrophy and sclerosis of the superior vena cava never equaled in extent and severity that seen in cases of chronic congestive heart failure.

COMMENT

Persistently increased tension in the vascular tree is generally accepted as the prime cause of vascular sclerosis. The order of sclerosis of the circulation may be listed as (1) arteriosclerosis of the greater circulation, (2) arteriosclerosis of the lesser circulation, (3) sclerosis of the venous system and (4) localized arteriosclerosis or phlebosclerosis. This order corresponds to the frequency of increased intravascular tension of the different parts of the circulation. In a given case it is not unusual, however, to see isolated phlebosclerosis in association with varicose veins of one leg or marked pulmonary arteriosclerosis or phlebosclerosis associated with mitral stenosis in a young person though the greater circulation is essentially intact.

It is well known that the tension in the superior vena cava is usually at or below zero and is raised above zero only in exceptional circumstances. In conditions in which the venous pressure in the liver is increased, as in portal cirrhosis, sclerosis of the hepatic veins is a common finding. In congestive heart failure the liver acts as a reservoir for the overloaded lungs. Consequently the hepatic veins and the superior and inferior venae cavae are chronically distended. As in sclerosis of the pulmonary artery and vein in pulmonary hypertension from mitral stenosis, the conditions in which there is chronic increase of tension in the hepatic veins are associated with phlebosclerosis of a high degree. The occurrence of phlebosclerosis at such sites of increased venous pressure favors the view that venous sclerosis also is due to increased tension in the vessel wall. Though phlebosclerosis is less common than arteriosclerosis, it is significant that in conditions in which venous pressure is increased over a long time phlebosclerosis occurs with great constancy.

In our material, though the degree of sclerosis of the superior vena cava paralleled roughly the degree of increased tension in the vessel wall, no exact correlation could be observed between either the severity or the duration of congestive heart failure and the degree of phlebo-

sclerosis. In some cases mild congestive failure or failure of short duration was observed with severe phlebosclerosis, while in others in which failure of either severe or long duration was noted, phlebosclerosis was relatively slight. The same fact holds, however, for hypertension of the greater or lesser circulation and arteriosclerosis. In these conditions there is also no exact correlation between vascular damage and the duration of increased tension. In another study [2] no exact correlation was possible between the degree of failure of the right side of the heart and the degree of associated sclerosis of the hepatic veins and inferior vena cava. It is possible that this disparity is due to varying degrees of anoxemia or to metabolic causes.

There is great similarity between arteriosclerosis and phlebosclerosis both in pathogenesis and in morbid anatomy. In arteriovenous aneurysm and fistula and in experimental arteriovenous anastomosis it may be shown that when the vein is put under increased tension or required to do increased work hypertrophy of its wall occurs. Eventually, atrophy of its wall occurs from nutritional impairment. In our findings the development of hypertrophy of the intima and of the smooth muscle of the media followed by atrophy supports the view of a similar mechanism. The view that the changes observed were due to increased tension from congestive heart failure is further supported by the fact that in the cases in which there was no failure the alterations were less marked or were isolated phenomena. It is significant that even in cases in which there was increased tension in the right side of the heart without failure the hypertrophy and sclerosis of the superior vena cava never equaled in extent or severity such impairment in cases of congestive heart failure. Since the degree of hypertrophy and sclerosis of the superior vena cava varied roughly in relation to the degree of increased tension of the right side of the heart, both the hypertrophy of the wall of the vein and its ultimate degeneration in congestive heart failure of long duration may be looked on as a response to increased tension.

SUMMARY

The superior venae cavae of 21 persons showing chronic congestive heart failure were studied and compared with those of a group showing hypertrophy of the right side of the heart without failure and with those of another group in whom there was no cardiac lesion at all.

In persons with chronic congestive heart failure associated with increased tension in the right side of the heart and in the superior vena cava, sclerosis of the superior vena cava is a common finding.

Histologically, the sclerotic process in the superior vena cava is characterized by hypertrophy of all the coats of the vein, most marked in the muscular layer of the media. These alterations are thickening

and scarring of the intima, splitting and reduplication of the internal elastic membrane and widening of the media with hypertrophy of the muscle cells and increase of collagen. Eventually, from increased tension and impairment of nutrition, fragmentation and replacement of muscle fibers occur.

Involvement of the superior venae cavae from persons not having congestive heart failure was slight and infrequent, and in not a single vein were all the coats of the vessel involved. Medial hypertrophy, which was so constant and marked in the superior venae cavae of the group who died in congestive heart failure, was an infrequent occurrence.

Phlebosclerosis and arteriosclerosis are similar in morbid anatomy and pathogenesis. The pathogenesis of sclerosis of the superior vena cava appears to be in prolonged increase of intravascular pressure.

EFFECT OF EXPERIMENTAL NEUTROPENIA ON THE HEALING OF WOUNDS*

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In a previous study[1] on a serum toxic to polymorphonuclear neutrophil leukocytes, it was shown that these cells could be greatly diminished in number or totally eliminated from the peripheral blood of guinea pigs. Repeated daily doses of increasing amounts of the antiserum maintained this condition for several days, after which a gradual increase in the number of the neutrophils occurred.

This finding led to speculation on the effect such neutropenia would have on the healing of wounds. Neutrophils are seen in large numbers about any area of injury to tissue, which has led some observers to believe that they play a part in the healing process. The object of our study was to test this hypothesis.

METHODS

Guinea pigs were used. Under aseptic precautions an incision was made through all layers of the abdominal wall and the edges of the wound were reapproximated using 000 plain catgut for the peritoneum and fascia recta and silk for the skin. Visceral wounds were tried, particularly wounds in the stomach, but were not as satisfactory as wounds in the abdominal wall. In one series the incisions were contaminated with Staphylococcus aureus in order that we might observe healing in the presence of infection.

After the animals were killed, an effort was made to determine the degree of healing with a machine testing tensile strength, but the wounds separated so easily that often no record could be obtained; hence these results were unreliable. The wounds were then ruptured with air pressure by slowly inflating the peritoneal cavity. A mercury manometer in the circuit gave the tension required for disruption. Microscopic sections were made through all layers of the wounds.

* Aided in part by a grant from the Committee on Scientific Research of the American Medical Association.

From the departments of medicine and surgery of the University of Rochester School of Medicine and Dentistry.

1. Chew, W. B.; Stephens, D. J., and Lawrence, J. S.: J. Immunol. **30**:301, 1936.

The antileukocytic serum was prepared, sterilized and standardized by the methods described.[1] It had been found that a dose of 0.5 cc., given intraperitoneally, was sufficient to produce neutropenia; so this amount was given as the initial dose to the majority of the animals. The dose was increased daily by amounts sufficient to keep the number of the neutrophils at a low level. In approximately one-half the animals, the initial injection of the antiserum was on the morning of operation, but in the majority of the other animals the initial injection was on the day preceding operation. In 2 instances, the administration of antiserum was begun two days before operation. In every instance, following the injection of the initial dose injections were given daily.

Sufficient white blood cell counts, total and differential, were made prior to operation to establish the normal values for each animal. Following operation, daily total and differential counts were made until the animal was put to death. The table gives the actual number of polymorphonuclear neutrophils prior to

Neutrophils Per Cubic Millimeter Before and After Operation

Guinea Pig	Before Operation*	Days After Operation 1	2	3	4	5	6	Comment
1	2,277	30	11					Injections begun day before operation
2	7,337	62	13	0				Injections begun day before operation
3	7,128	450	0	0				Injections begun day of operation
4	4,945	216	0	59				Injections begun day of operation
5	10,807	700	243	81	61			Injections begun day before operation
6	2,756	0	0	0	35			Injections begun day of operation
7	4,644	21	0	0	0			Injections begun day of operation
8	1,131	0	108	192	60			Injections begun day of operation
9	6,070	765	78	28	360	1,193		Injections begun 2 days before operation
10	2,160	0	0	0	0	72		Injections begun day of operation
11	6,020	5,986	333	0	19	0		Injections begun day of operation
12	2,748	138	0	400	0	100	845	Injections begun day of operation
13	3,524	30	16	21	196	122	273	Injections begun 2 days before operation
14	2,888	82	47	246	51	61		Injections begun day of operation
15	7,285	234	140	168	451			Injections begun day before operation (infected)
16	2,484	0	0					Injections begun day before operation
17	6,165	0						Injections begun day before operation
18	2,496	0						Injections begun day before operation

* Figures in this column represent those obtained for each animal in the last determination prior to the injection of antiserum.

operation and on each day after operation. While there are a few exceptions, it will be noted that the level of neutrophils was kept very low following operation. Such neutropenia is difficult to maintain longer than six days owing to the fact that the amount of antiserum required to produce it increases progressively with each day. Accordingly, observations were not carried beyond this length of time. It is felt that this period is sufficient for observation of the essentials of the healing process but of course not for following it to its completion.[2]

RESULTS

Forty-two guinea pigs were used; half of these were given antiserum, and the remainder were used for controls.

One series of 34 animals, 17 of which had been rendered neutropenic, were operated on under aseptic precautions. The gross appearance of the wounds of the treated guinea pigs did not differ from those of the

2. Harvey, S. C.: Arch. Surg. **18**:1227, 1929.

untreated animals. The tensile strength as measured by the air pressure required to disrupt the wounds varied over wide limits. The average disrupting force was 132 mm. of mercury for the neutropenic and

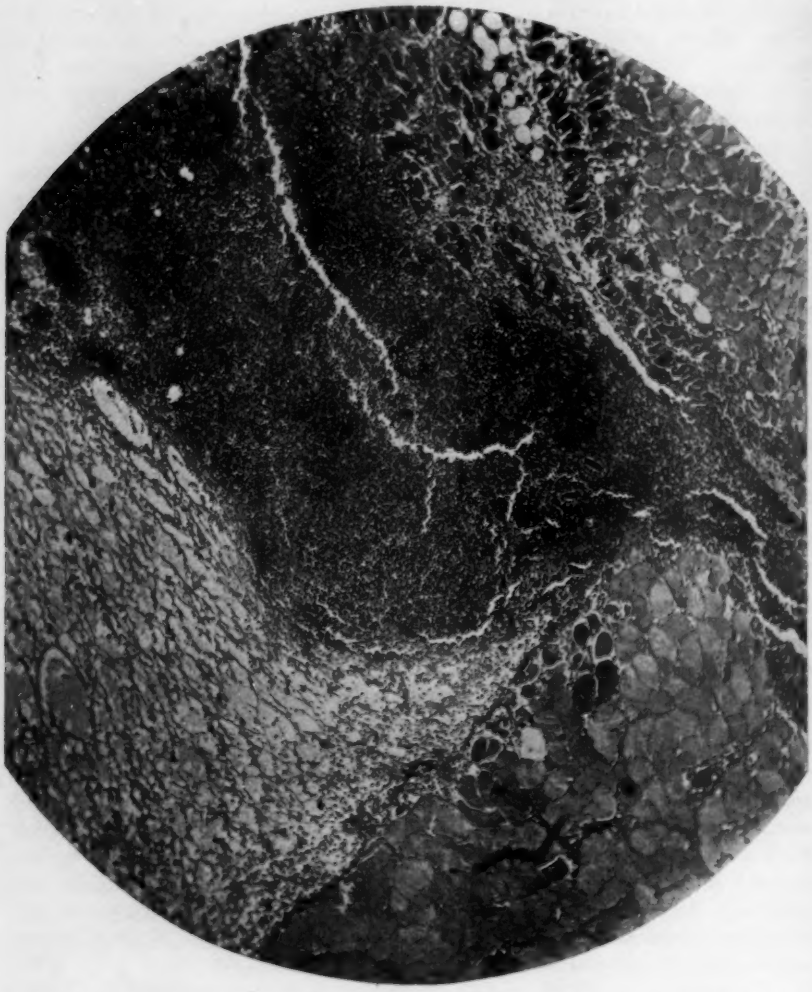

Fig. 1.—Photomicrograph of an infected wound in a normal control guinea pig. Note the accumulation of large numbers of polymorphonuclear neutrophils.

196 mm. for the control animals. The difference was not considered significant in this small group.

In judging repair, the greatest reliance was placed on the histologic appearance of the healing process. This was quite different in the two

groups, the striking contrast lying in the reduction or absence of neutrophils in the treated animals, which, nevertheless, had as much fibroblastic proliferation as the controls. Fibroplasia and repair occurred

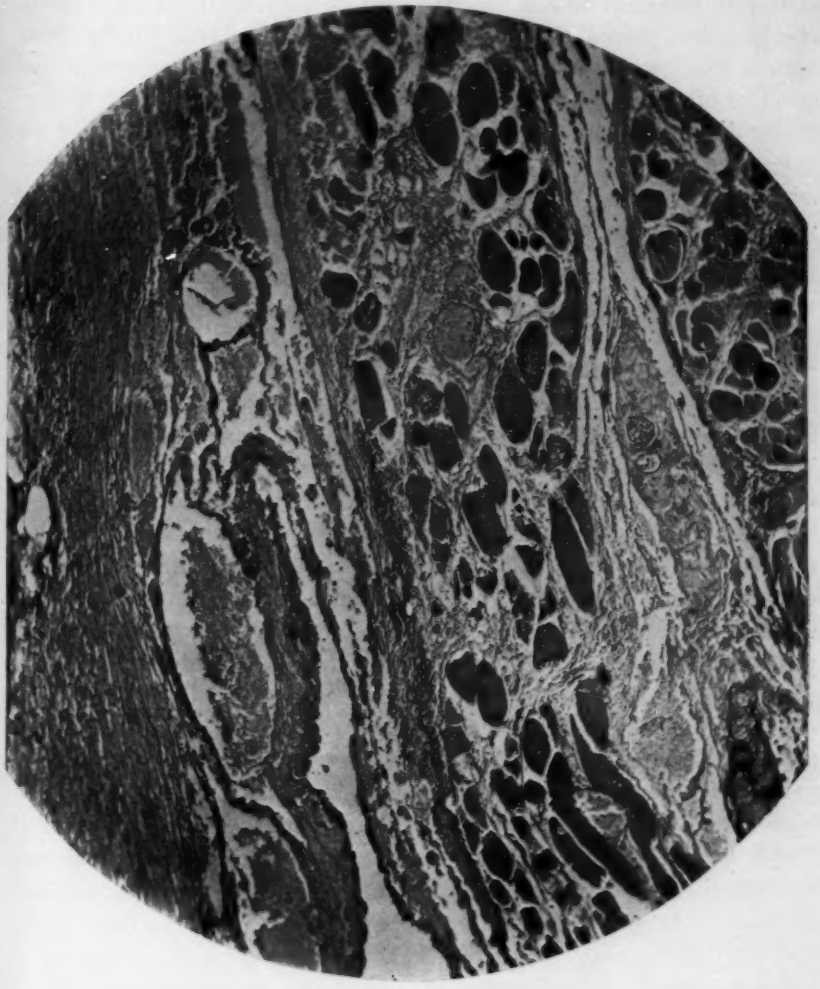

Fig. 2.—Photomicrograph of an infected wound in a neutropenic guinea pig. No polymorphonuclear neutrophils are present.

equally well in the presence or in the absence of polymorphonuclear leukocytes in the wounds.

A few of both the treated and the control animals showed occasional bacteria in the tissues, though there was no gross evidence of infection

in any of the wounds in these animals. The appearance differed here also, for in the neutropenic guinea pigs there were few if any leukocytes about the bacteria, while the controls showed the usual defense reaction of aggregations of polymorphonuclear cells. This led to a trial of deliberate infection of the wounds with Staph. aureus at the time of operation in 8 guinea pigs. These neutropenic animals had little defense against this insult. With but a single exception, they presented diffuse cellulitis of the abdominal wall, injection of the peritoneum and hemorrhagic discharge from the wounds. The microscopic appearance of the tissue was not unlike postmortem degeneration with necrosis of tissue—many bacteria but few cells. The control animals responded in the usual way, with localization of the infection to form an abscess, in which were found masses of leukocytes.

COMMENT

It appears from the results stated that the polymorphonuclear neutrophil plays a part in the repair of wounds only so far as it helps to combat suppuration. The essential feature of repair is fibroplasia, and this process is apparently independent of the neutrophilic leukocyte. This indirectly supports the concept that the fibroblasts may originate by metaplasia from the lymphocytes or macrophages.

Some histologists have thought that the polymorphonuclear leukocytes liquefied the fibrin in the wound and so paved the way for ingrowth of fibroblasts. In this way they were considered an essential factor in the reparative process. This is apparently incorrect, for fibroplasia progressed normally when there were few if any neutrophils in the wounds.

It is worthy of comment that guinea pigs with so few neutrophils as reported in this paper did not contract gross infection during the period of observation. That they were more susceptible to infection than normal animals was shown by the response to virulent cultures of Staph. aureus put into the wounds. However, with aseptic technic the wounds did not get infected. Further, we have never noted oral, perianal or other types of spontaneous infection in guinea pigs kept neutropenic for varying periods. This indicates that the neutropenic guinea pig is less susceptible to infection than the neutropenic human subject.

SUMMARY

Healing of aseptic wounds in guinea pigs has been shown to be unaffected by the presence or the absence of neutrophils.

In neutropenic guinea pigs that have septic wounds there is marked inability to cope with the healing process.

SO-CALLED BILIARY CIRRHOSIS

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Since the beginning of knowledge of hepatic cirrhosis, the subject has been in turmoil. Major [1] gave credit to John Brown for being the first to describe a cirrhotic liver, in 1685. Brown [2] at necropsy on a patient with marked ascites noted the "glandulous appearance" of the liver. He illustrated this description with a picture of a coarsely nodular liver. Laennec [3] introduced the term "cirrhosis of the liver" in 1826. It is of particular interest that he recognized that "this type of growth belongs to the group of those which are confused under the name of Scirrhus. I believe we ought to designate it with the name of cirrhosis, because of its color." In addition he stressed the fact that there was progressive atrophy and observed that similar changes occurred in other organs. Webster's "New International Dictionary" derives the term "cirrhosis" from the Greek word *kirrhos,* meaning orange colored. It is not strange, but it is confusing and unfortunate, that in general "cirrhosis" has become almost synonymous with "fibrosis." Kaufmann [4] observed that "cirrhosis," meaning yellow, was a name applied first to the contracted liver and that later it was applied generally to organ-shrinking processes which are accompanied by more or less formation of connective tissue, such as cirrhosis of the lung or of the kidney, and that the color was then ignored.

Even as the original description of hepatic cirrhosis offers little help in defining the disease, so the current conceptions of the disease differ too widely to be of any help. Mallory [5] applied the term "cir-

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* Fellow in Medicine of the Mayo Foundation at the time this work was done.

1. Major, R. H.: Classic Descriptions of Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932, pp. 597-602.

2. Brown, J.: Phil. Tr. Roy. Soc., London **3**:248, 1685.

3. Laennec, R. T. H.: Traité de l'auscultation médiate et des maladies des poumons et du cœur, ed. 2, Paris, J. S. Chaudé, 1826, vol. 2, pp. 187-197.

4. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, pp. 921-928 and 954-955.

5. Mallory, F. B.: Bull. Johns Hopkins Hosp. **22**:69, 1911.

rhosis" "to all sclerosed conditions of the liver, whether progressive or not, in which destruction of liver cells is associated with real or apparent increase of connective tissue." Emphasis is clearly laid on parenchymal destruction and fibrosis.

Rössle [6] stated that "it can be said that liver cirrhosis is due to three main factors: destruction of liver tissue, scar tissue formation and compensatory hyperplasia, or regeneration, respectively, and therefore in spite of various etiologic factors and different appearances it might be considered a disease entity." The prominence of these individual features varies in the different types of "cirrhosis." In his discussion he stressed the fibrosis and parenchymal damage. He recognized that parenchymal regeneration may occur but did not require its presence. Eppinger [7] quoted Rössle frequently and apparently endorsed his opinion.

Kaufmann,[4] speaking of the common atrophic cirrhosis of the liver, stated that "this form of chronic hepatitis depends on a marked connective tissue development with destruction of considerable liver tissue." He further added that parenchymal hyperplasia, even nodular or adenomatous in character, may occur in some cirrhoses.

Bell [8] stated that "cirrhosis (of the liver) is a very slowly progressing degenerative and reparative process, apparently inflammatory in nature, involving the entire organ and characterized by a definite increase of the portal connective tissue with or without an increase of the intralobular connective tissue." In his discussion of the microscopic features of portal cirrhosis he further stated that "the proliferation of these structures (the newly formed bile ducts) is at times so extensive as to produce rounded, grossly visible, pale nodules, the so-called adenomata." He gave credit to both the interlobular bile ducts and the parenchymal remnants for the formation of the parenchymal nodules.

MacCallum [9] defined cirrhosis of the liver as "a term applied to an extensive diffuse scarring of the liver which has followed the destruction of much of the liver substance. It is regularly accompanied by widespread regeneration of the functional liver tissue, usually sufficient to prevent the appearance of any signs of hepatic insufficiency." In

6. Rössle, R.: Entzündungen der Leber, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 5, no. 1, pp. 284, 286-313, 376-405 and 429-452.

7. Eppinger, H.: Die Leberkrankheiten: Allgemeine und spezielle Pathologie und Therapie der Leber, Berlin, Julius Springer, 1937, pp. 121, 148 and 571-598.

8. Bell, E. T.: A Text-Book of Pathology, ed. 3, Philadelphia, Lea & Febiger, 1938, pp. 688-695.

9. MacCallum, W. G.: A Text-Book of Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1936, pp. 304-316.

his discussion of the microscopic features of diffuse nodular cirrhosis (Laennec's cirrhosis) he stressed the disruption of the lobular architecture by nodular hyperplasia. He further stated that "although many confiicting views have been held, it seems clear that the injurious agent effects the destruction of the liver cells in the first instance, and that the scarring and the hyperplasia of the epithelial remnants are reparatory processes."

From these brief references to several authorities it is clear that a definition of hepatic cirrhosis acceptable to all is difficult to find. There is general agreement that parenchymal destruction and scarring must be present. There is less agreement on the importance of parenchymal repair. When only parenchymal destruction and scarring are required by definition of hepatic cirrhosis, it is difficult to rule out certain conditions recognized as not generally deserving of the designation "hepatic cirrhosis."

Many agents often produce obvious parenchymal destruction and at least an apparent increase in connective tissue. Of the chemical agents, cinchophen may be mentioned, and of the physiologic disturbances, severe chronic passive congestion, hyperthyroidism and even biliary obstruction may be mentioned. However, these factors are not regarded as frequent causes of cirrhosis of the liver. The ill defined yellow atrophy of the liver is not and should not be classified ordinarily as hepatic cirrhosis, although parenchymal destruction and an apparent increase in connective tissue are commonly present.

In brief, a definition including simply parenchymal destruction and scarring seems too broad. Such a definition apparently includes lesions which it does not seem justifiable to classify under hepatic cirrhosis. Hence, for the purpose of this study, hepatic cirrhosis is defined as including parenchymal degeneration, fibrosis and nodular parenchymal repair.

In this investigation the primary interest lies, not in the general subject of hepatic cirrhosis and the multiple subtypes of this disease, but in the subject of so-called biliary cirrhosis. This term, fostered by the French, has gained some recognition in Germany and is frequently used by pathologists and clinicians on this continent. The features of biliary cirrhosis will be presented subsequently, but it may be said here that clearly this type of disease of the liver as usually described is to be excluded according to the foregoing definition of hepatic cirrhosis.

The definition of hepatic cirrhosis given seems in accord with the views of MacCallum.[9] However, in his discussion of obstructive biliary "cirrhosis" he did not mention parenchymal repair. One can hardly say that he suggested it may occur when he stated: "Apparently in

the cases of longest duration (prolonged biliary obstruction), a great deal more distortion of the liver may occur, but it does not approach that seen in the previous type (diffuse nodular cirrhosis)."

LITERATURE

General interest in the possibility of hepatic cirrhosis following biliary obstruction received its main impetus from the clinical and experimental observations of Charcot and Gombault [10] and Charcot.[11] They postulated cirrhosis of biliary origin in contradistinction to that of portal origin. However, the foundations for their postulate had been laid by the reports of Jones,[12] Wyss,[13] Leyden,[14] Mayer,[14] Green [15] and Legg.[16] The earlier cases were reviewed by Mangelsdorf [17] and Ford,[18] but since then a vast literature on the subject has accumulated.

Pure biliary stasis has been regarded as sufficient to produce "biliary cirrhosis" by Quincke,[19] Richardson,[20] Ogata,[21] Lieber and Stewart,[22] MacMahon and Mallory [23] and others. Litten,[24] Nasse,[25] Ford,[18] Rössle [6] and others have emphasized the importance of infection or inflammation within the biliary tract in the production of this disease. Beloussow,[26] Rolleston,[27] and Eppinger [7] were not convinced that biliary obstruction resulted in cirrhosis in man. Senator,[28] Ford [18] and Kauf-

10. Charcot, J. M., and Gombault, A.: Arch. de physiol. norm. et path. **3**:272, 1876.

11. Charcot, J. M.: Leçons sur les maladies du foie, des voies biliaires et des reins, Paris, aux bureaux du Progrès médical, 1877, pp. 160-166 and 205-218.

12. Jones, H.: Tr. Path. Soc. London **5**:146, 1854.

13. Wyss, O.: Virchows Arch. f. path. Anat. **35**:553, 1866.

14. Cited by Legg.[16]

15. Green, T. H.: Tr. Path. Soc. London **23**:133, 1872.

16. Legg, J. W.: St. Barth. Hosp. Rep. **9**:161, 1873; Tr. Path. Soc. London **25**:133 and 155, 1874.

17. Mangelsdorf, J.: Deutsches Arch. f. klin. Med. **31**:522, 1882.

18. Ford, W. W.: Am. J. M. Sc. **121**:60, 1901.

19. Quincke, H.: Diseases of the Liver, Pancreas, and Suprarenal Glands, in Nothnagel, H.: Encyclopedia of Practical Medicine, translated by A. Stengel, Philadelphia, W. B. Saunders Company, 1903, pp. 431 and 727-729.

20. Richardson, M. L.: J. Exper. Med. **14**:401, 1911.

21. Ogata, T.: Beitr. z. path. Anat. u. z. allg. Path. **55**:236, 1913.

22. Lieber, M. M., and Stewart, H. L.: Arch. Path. **17**:362, 1934.

23. MacMahon, H. E., and Mallory, F. B.: Am. J. Path. **5**:645, 1929.

24. Litten, M.: Charité-Ann. **5**:153, 1880.

25. Nasse: Arch. f. klin. Chir. **48**:885, 1894.

26. Beloussow, P. N.: Arch. f. exper. Path. u. Pharmakol. **14**:200, 1881.

27. Rolleston, H. D.: Diseases of the Liver, Gall-Bladder and Bile-Ducts, Philadelphia, W. B. Saunders Company, 1905, pp. 326-332.

28. Senator, H.: Berl. klin. Wchnschr. **30**:1233, 1893.

man [29] recognized obstructive "biliary cirrhosis" and stated that biliary obstruction in man may lead to later hepatic shrinkage or atrophy. Janowski [30] held that death would occur before hepatic contraction resulted. Judd and Counseller,[31] Greene and his co-workers [32] and Weir and Snell [33] found what they called obstructive biliary cirrhosis was more frequently associated with benign than with neoplastic obstructive biliary lesions.

Numerous investigators have credited the experimental ligation of the extrahepatic bile ducts with the production of "biliary cirrhosis," as did Charcot and Gombault,[10] Harley and Barratt,[34] Richardson,[20] Ogata,[21] Rous and Larimore,[35] MacMahon, Lawrence and Maddock,[36] Moon [37] and others. Similar procedures studied by Litten,[24] Gerhardt,[38] Cameron and Oakley,[39] Bollman and Mann [40] and others were not specifically interpreted as producing "biliary cirrhosis." Quincke,[19] Ogata [21] and Zypkin [41] were reluctant to apply such conclusions from animal experimentation to man, whereas MacMahon and Mallory [23] were inclined to regard the results in man and animals as essentially similar. Of particular interest is the report of Snell, Greene and Rowntree [42] in which they described ascites, extensive collateral circulation and monolobular hepatic fibrosis occurring in 2 dogs after prolonged ligation of the common duct.

Perhaps the most comprehensive recent review of the subject of "biliary cirrhosis" is that of Rössle.[6] He recognized cholostatic "biliary cirrhosis" (due to pure stasis of bile), the more frequent cholangitic "biliary cirrhosis" (due to bile stasis with superimposed infection) and the infrequent cholangiolitic "biliary cirrhosis" (due to toxic alterations of the smallest bile ducts).

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29. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, ed. 6, Berlin, G. Reimer, 1911, pp. 593-594.
30. Janowski, W.: Beitr. z. path. Anat. u. z. allg. Path. **11**:344, 1892.
31. Judd, E. S., and Counseller, V. S.: J. A. M. A. **89**:1751, 1927.
32. Greene, C. H.; McVicar, C. S.; Snell, A. M., and Rowntree, L. G.: Arch. Int. Med. **40**:159, 1927.
33. Weir, J. F., and Snell, A. M.: Am. J. Digest. Dis. & Nutrition **3**:629, 1936.
34. Harley, V., and Barratt, W.: J. Path. & Bact. **7**:203, 1901.
35. Rous, P., and Larimore, L. D.: J. Exper. Med. **32**:249, 1920.
36. MacMahon, H. E.; Lawrence, J. S., and Maddock, S. J.: Am. J. Path. **5**:631, 1929.
37. Moon, V. H.: Arch. Path. **18**:381, 1934.
38. Gerhardt, D.: Arch. f. exper. Path. u. Pharmakol. **30**:1, 1892.
39. Cameron, G. R., and Oakley, C. L.: J. Path. & Bact. **35**:769, 1932.
40. Bollman, J. L., and Mann, F. C.: Ergebn. d. Physiol. **38**:445, 1936.
41. Zypkin, S. M.: Virchows Arch. f. path. Anat. **262**:791, 1926.
42. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Arch. Int. Med. **40**: 471, 1927.

Several series of necropsies have demonstrated that so-called biliary cirrhosis following obstruction of the bile ducts is relatively infrequent. Ophüls [43] reported the incidence to be 0.43 per cent; Mallory,[44] 0.29 per cent, and Schumacher,[45] 0.40 per cent.

MATERIAL AND METHODS

The cases in this series were chosen from the necropsy material of the section on pathologic anatomy of the Mayo Clinic covering the period from July 1, 1922, to June 30, 1938, inclusive. During this time there were 8,986 necropsies, covering all age groups.

Only those cases were selected in which necropsy showed biliary obstruction and obstructive jaundice. A group of 244 cases (2.7 per cent of the total number in which necropsy records were available) fulfilled these requirements. The records of these cases were reviewed, particular attention being given to (1) the course of the jaundice, (2) any clinical suggestion of antecedent hepatic parenchymal disease, (3) the gross appearance of the liver and biliary tract and (4) any evidence of portal obstruction, such as esophageal varices and ascites. Note was made of the presence of hepatic metastasis, suppurative cholangeitis with abscess formation, pylephlebitis, hepatic vascular lesions, peritonitis, chronic passive congestion and other lesions. These lesions did not serve to exclude cases from the series, since such lesions do not, as a rule, induce hepatic changes which confuse the picture of true hepatic cirrhosis.

The important part of the problem centered about the microscopic studies. It was felt that ultimately the diagnosis of cirrhosis must rest on histologic study. The routine tissue sections of the liver, biliary passages and obstructive biliary lesion, stained with hematoxylin and eosin, were studied. Ordinarily these sections were entirely adequate, but in many instances they were supplemented by other sections from the liver stained by the Van Gieson, Mallory-Heidenhain and Perdrau technics for connective tissue.

OBSERVATIONS AND RESULTS

In this group of 244 cases in which necropsy showed biliary obstruction and obstructive jaundice, almost every type of obstructive biliary lesion was represented. Some form of neoplastic obstruction was present in 64.3 per cent (157 cases). In only 35.7 per cent (87 cases) could the disease be classified as due to a benign type of obstruction. In 48.3 per cent (42 cases) of the latter group the obstruction was due to choledocholithiasis, and in 44.8 per cent (39 cases), to postcholecystectomy stricture.

It was found that the cases could quite easily be grouped into those in which the jaundice, even though fluctuating, was continuously present from its first appearance and those in which the jaundice was intermittently present, i. e., in which there were at least two episodes of

43. Ophüls, W.: A Statistical Survey of Three Thousand Autopsies, Stanford University, Calif., Stanford University Press, 1926, pp. 275, 286 and 302.

44. Mallory, F. B.: New England J. Med. **206**:1231, 1932.

45. Schumacher, G. A.: Am. J. M. Sc. **194**:693, 1937.

jaundice separated by a period in which visible icterus had apparently cleared. Jaundice was continuous in 78.7 per cent (192 cases). In 73.4 per cent (141 cases) of this group the jaundice was associated with neoplastic obstruction whereas in 26.6 per cent (51 cases) it was secondary to benign obstruction. In only 18 per cent (44 cases) was the jaundice intermittent; in 25 per cent of these (11 cases) it was due to neoplastic obstruction, and in 75 per cent (33 cases) it was due to benign obstruction. Eight cases, or 3.3 per cent, could not be definitely included in either group. It is of particular interest that of the 11 cases in which intermittent jaundice was associated with neoplastic obstruction, the obstruction in 7 was due to carcinoma of the ampulla of Vater.

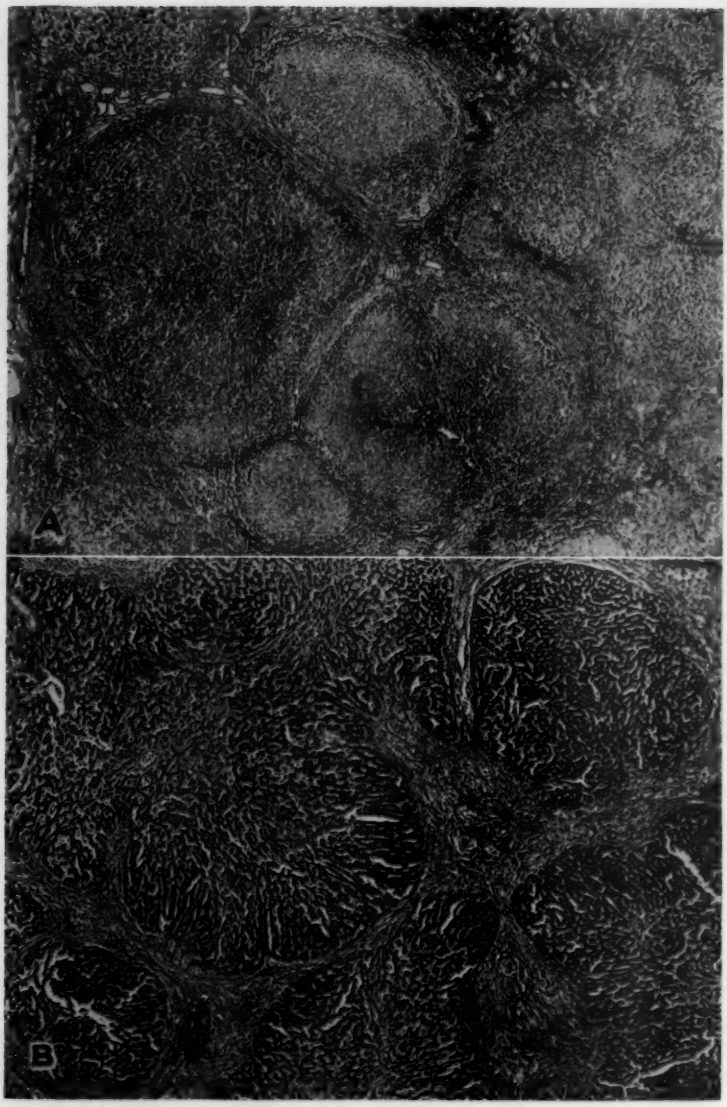
There was a definite difference between these two groups in respect to the duration of life after the first appearance of jaundice. In the group with persistent jaundice 87.9 per cent (124 patients) of those with neoplastic obstruction and 70.6 per cent (36 patients) of those with benign obstruction died within three months after the onset of jaundice. In the group with intermittent jaundice 54.5 per cent (6 patients) of those with a neoplastic obstruction and 54.5 per cent (18 patients) of those with a benign obstruction died more than one year after the first appearance of jaundice.

In this series of 244 cases in which necropsy showed biliary obstruction and obstructive jaundice, true hepatic cirrhosis was present in 8.6 per cent (21 cases). The criteria for this diagnosis have already been set forth as including parenchymal atrophy, fibrosis and nodular parenchymal regeneration.

The obstructing lesion in 10 of these 21 cases was postcholecystectomy stricture, in 6 choledocholithiasis, in 2 carcinoma of the ampulla of Vater, in 1 carcinoma of the gallbladder with invasion of the common duct, in 1 carcinoma of the head of the pancreas and in 1 recurrent carcinoma of the stomach with invasion of the common duct.

There were 7 men and 14 women with true hepatic cirrhosis. There were 4 men in the group with neoplastic obstruction and 3 with choledocholithiasis. The average age of those with postcholecystectomy strictures was 40 years; of those with choledocholithiasis, 57 years, and of those with neoplastic obstruction, 62 years. The average age for the entire group was 50 years.

It is of particular interest that 71.4 per cent (15 patients) of the 21 patients gave a history of intermittent obstructive jaundice. Every patient with benign obstruction gave a history of intermittent jaundice except a patient in the group with postcholecystectomy stricture and another in the group with choledocholithiasis. It is also of interest that the average duration of life after the first appearance of jaundice was 3.8 years for the patients with benign obstruction, 0.5 year for those with neoplastic obstruction and 3 years for the entire group.



A, cirrhosis (with portal obstruction, varices with hemorrhage and ascites) from biliary obstruction; × 25. Recurrent postoperative stricture of the common duct with obstructive jaundice (occurring intermittently for 8 years). *B*, cirrhosis from biliary obstruction; × 25. Recurrent postoperative stricture of the common duct with obstructive jaundice (occurring intermittently for 49 months).

In the livers of these patients with true hepatic cirrhosis there were the usual gross changes associated with biliary obstruction. A granular or nodular surface was present in 13. Two patients had esophageal varices with serious hemorrhage and ascites. Two patients had well developed collateral venous circulation elsewhere with ascites. In 2 other patients there was ascites without demonstrable varices. One of these also had carcinomatosis of the peritoneum.

Microscopically, the architecture of these livers was altered, sometimes to a marked degree. There were widespread parenchymal degenerative changes, commonly most marked about the central vein but frequently focal and occasionally peripheral. Sometimes actual necrosis was present. It was not unusual to see isolated groups of parenchymal cells in the portal connective tissue. There was a moderate to marked increase in the portal connective tissue, and it was not unusual to see intralobular extension. Particularly noteworthy in these specimens were the evidences of parenchymal regeneration. This had taken place to a degree deserving of the term nodular. In these nodules the sinusoidal pattern and vascular relationships were altered. Bile thrombi were present in every case, and frequently parenchymal and reticuloendothelial cells contained bile pigment. Commonly there was at least an apparent increase in the interlobular bile ducts. Collections of lymphocytes or polymorphonuclear leukocytes were frequently present. Two typical cases are illustrated (figure).

In one of these cases there was a history of a moderate use of alcohol. In another there was concurrent mild exophthalmic goiter. Neither of these factors was regarded as sufficient to influence the hepatic changes found. Syphilis was ruled out by the Kolmer or the Kline and the Kahn test in all but a single case. In the latter case there was nothing in the clinical or necropsy records to suggest syphilis. In an additional case there was a six year history of dyspepsia, colic and vague spells of pruritus. Finally there was jaundice for two months, and at necropsy a carcinoma of the common duct was encountered. This case was discarded because of the suggestion of antecedent portal cirrhosis. The past histories of the other cases were entirely negative in this respect.

COMMENT

In a review of the extensive literature it appears that so-called biliary cirrhosis is recognized by its proponents in livers which have endured biliary stasis and which have parenchymal degenerative changes of various sorts, an increase in the portal connective tissue, an apparent increase in the interlobular ducts, bile thrombi and collections of cells, such as lymphocytes and polymorphonuclear leukocytes, in the portal connective tissue. Emphasis is clearly laid on bile stasis, parenchymal degeneration and fibrosis of some degree.

That these changes are commonly associated with biliary obstruction in man and in experimental animals is not doubted. In our study of 244 cases in which necropsy showed biliary obstruction and obstructive jaundice it was found that most of the changes listed in the foregoing paragraph were almost always present.

The outstanding feature in the liver which has endured biliary obstruction is parenchymal degeneration. Quincke [19] emphasized this pertinent point. Similarly, the results of parenchymal degeneration frequently dominate the clinical picture. It is for this reason that experience dictates a guarded prognosis for these patients unless the biliary obstruction can be relieved and hepatic recovery permitted. Quincke [19] and Rolleston [27] were inclined to regard the interstitial proliferation as of only histologic interest and without influence on the clinical course of the disease. Eppinger [46] interpreted the late picture of uncomplicated obstructive jaundice as primarily one of parenchymal atrophy with condensation of connective tissue. Certainly a diagnosis of biliary cirrhosis according to the current concept of the term adds little to the interpretation of either the clinical or the pathologic picture. It seems that conditions of this type might be described more suitably as hepatic atrophy. This term would place the emphasis where it may rightfully belong: on the parenchymal degeneration which is associated with biliary obstruction and jaundice. Further, it is appreciated clinically that at least certain phases of hepatic function are impaired in the presence of obstructive jaundice, even though there are recognized limitations to the clinical tests of hepatic function. The term "hepatic atrophy" would be compatible with an impairment of hepatic function and might even imply it. It should not be confusing to speak of hepatic atrophy in the presence of a normal or greater than normal weight of the liver since such an organ enduring obstructive jaundice can still be atrophic to microscopic examination and be impaired in its physiologic functions. The latter factors seem more important fundamentally than the gross weight of the liver, which is notoriously unpredictable and frequently difficult to evaluate in considering the course of the disease in retrospect.

In this study 21 cases of a condition consisting in biliary obstruction, obstructive jaundice and true hepatic cirrhosis were found. The criteria for the latter diagnosis have been stated. It is clear that there is a definite distinction between these cases and cases of what is called "biliary cirrhosis" in the literature. The distinctive feature is the nodular parenchymal regeneration which is present in addition to the parenchymal atrophy and fibrosis. Just as progressive hepatic parenchymal degeneration may lead to death, so may sufficient parenchymal regeneration conceivably prevent an untimely death.

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46. Eppinger, H.: Beitr. z. path. Anat. u. z. allg. Path. **31**:230, 1902; footnote 7.

It is of particular interest concerning the 21 cases of biliary obstruction, obstructive jaundice and true hepatic cirrhosis that there was a history of intermittent jaundice in 71.4 per cent (15 cases). The average duration for the entire group from the first appearance of jaundice to death was 3 years. The combination of these facts suggests intermittent episodes of parenchymal destruction over a relatively long period with intervals of relief from jaundice, permitting an opportunity for parenchymal repair. Theoretically, at least, intermittent destruction and intermittent repair present a favorable situation for the production of true hepatic cirrhosis.

In the remaining cases, 28.6 per cent (6 cases), there was continuous jaundice. The jaundice was fluctuating in 4 of these cases and only mild to moderate in 2. The average duration from the first appearance of jaundice to death in these cases was a little over 0.6 year. It is apparent that parenchymal regeneration may occasionally occur in the presence of continuous obstructive jaundice.

It has occasionally been stated in the literature that biliary obstruction, obstructive jaundice and hepatic cirrhosis of the Laennec type may infrequently occur together. Litten,[24] Janowski,[30] Quincke,[19] Rolleston,[27] Karsner [47] and others have expressed such an opinion. Ford [18] even regarded "hepatic contraction" with ascites and venous collateral circulation as relatively frequent in "biliary cirrhosis." The objection might well be raised that the entire group of 21 cases presents two concurrent but unrelated lesions, namely, hepatic cirrhosis and biliary obstruction. One case has been mentioned in a previous section of this paper which was ruled out because this seemed possible. Recently Bloomfield [48] graphically reemphasized the fact that hepatic cirrhosis of the Laennec type is commonly latent and asymptomatic "until the final crash of hepatic insufficiency." Hence the possibility that the hepatic cirrhosis was present before the onset of biliary obstruction cannot be denied. It would be of great interest to know the state of the liver at the time of the initial operation in the patients in whom postcholecystectomy stricture and true hepatic cirrhosis subsequently were found. Unfortunately, these patients without exception originally were operated on elsewhere.

It is of indirect value to refer to the incidence of hepatic cirrhosis of all types in persons examined post mortem. Ophüls [43] reported an incidence of 5.5 per cent; Mallory,[44] 5.9 per cent, and Schumacher,[45] 3.7 per cent. Rössle [6] cited a number of other series, including his own, in which the highest incidence of cirrhosis was 4 per cent.

47. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, 1926, p. 682.

48. Bloomfield, A. L.: Am. J. M. Sc. **195**:429, 1938.

It is of interest that the incidence of hepatic cirrhosis in this series of cases of biliary obstruction and obstructive jaundice is 8.6 per cent. This is perhaps significantly greater than the incidence of hepatic cirrhosis of all types in the usual necropsy series.

These data suggest that the relationship between biliary obstruction, obstructive jaundice and true hepatic cirrhosis may be more than coincidental. It is suggested that in such cases the condition be called "cirrhosis from biliary obstruction" and that the phrase "biliary cirrhosis" be dropped as confusing and misleading.

SUMMARY

It is suggested that hepatic cirrhosis be defined as including parenchymal degeneration, fibrosis and nodular parenchymal regeneration.

From a series of 244 cases of biliary obstruction and obstructive jaundice, 21 cases, or 8.6 per cent, were separated out in which these conditions were associated with hepatic cirrhosis as defined in the foregoing paragraph. In 10 of these 21 cases the biliary obstruction was due to postoperative stricture of the common duct, in 6 cases to choledocholithiasis, in 2 cases to carcinoma of the ampulla of Vater and in 3 cases to other malignant lesions.

An intermittent type of obstructive jaundice was present in 15 of these 21 cases, or 71.4 per cent. The average case duration from the first onset of jaundice to death was 3 years. These factors may be involved in the production of regeneration in these cases.

It is suggested that the term "biliary cirrhosis" be dropped and that for the infrequent combination of biliary obstruction, obstructive jaundice and true hepatic cirrhosis the designation "cirrhosis from biliary obstruction" be employed.

Cases in which hepatic parenchymal damage without signs of regeneration follows obstruction of the bile ducts should be classified as instances of hepatic atrophy.

EFFECT OF THOROTRAST (COLLOIDAL THORIUM DIOXIDE) ON EPENDYMAL LINING AND RELATED PARTS OF THE BRAIN

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Thorotrast,[1] a colloidal preparation of thorium dioxide, is recommended by some as a contrast medium for ventriculographic work preferable to air. Radovici and Meller [2] were the first to use thorotrast for the visualization of the ventricular cavities. They described their observations in a series of papers in which they expressed the opinion that the elimination of this substance from the cerebrospinal pathways was carried out by way of the blood stream and lymphatics. In their later reports they concluded that this elimination at best must be very slow, and by roentgen and histologic studies they demonstrated the persistence of thorotrast in the ventricular system of monkeys a year after injection. In their investigations they described the accumulation of this substance in the subarachnoid spaces and its adherence to the ependymal surface, and they emphasized the absence of penetration into the parenchyma of the brain and the absence of perivascular reaction. In a more recent contribution [2c] they described thorotrast as a completely inert substance, but on the basis of its slow elimination and the changes it obviously produced in the brain they advised extreme caution in its use as a diagnostic medium. Jacobi, Löhr and Wustmann,[3] however, considered the use of thorotrast in its present form to be a safe procedure. Freeman and his co-workers [4] also favored the use of thorotrast for the purpose under consideration and reported that one of their patients showed no clinical evidence of harmful effects twenty months after the

From the Laboratories of the Mount Sinai Hospital.

1. Thorotrast, preliminary report of the Council on Pharmacy and Chemistry, J. A. M. A. **99**:2183, 1932.

2. (*a*) Radovici, A., and Meller, O.: Bull. Acad. de méd., Paris **107**:314, 1932; (*b*) Presse méd. **40**:1933, 1932; (*c*) Rev. neurol. **1**:541, 1933. (*d*) Radovici, A.; Bazgan, I., and Meller, O.: Compt. rend. Soc. de biol. **114**:207, 1933. (*e*) Radovici, A., and Meller, O.: Presse méd. **42**:153, 1934.

3. (*a*) Wustmann, O.: Deutsche Ztschr. f. Chir. **238**:530, 1933. (*b*) Jacobi, W.; Löhr, W., and Wustmann, O.: Ueber die Darstellung des zentralen und peripheren Nervensystems im Röntgenbild, Leipzig, Johann Ambrosius Barth, 1934.

4. Freeman, W.; Schoenfeld, H. H., and Moore, C.: J. A. M. A. **106**:96, 1936.

injection. In a more recent study Freeman [5] investigated human brains coming to autopsy at different periods after the injection of thorotrast. He found that the earliest changes, which became evident within an hour after the introduction of thorotrast, were swelling of the epithelium of the choroid plexus and adherence of granules of thorotrast to its surface. In a brain which came to autopsy twenty-four hours after the injection of thorotrast a leukocytic infiltration with some destruction of the epithelium of the choroid plexus was noted. The ependyma, at this time, showed beginning exfoliation and an aggregation of macrophages and leukocytes over the free surface of the ependymal lining. The later development of the process is not clear from the description given by Freeman. He stressed the fact that in the presence of obstructive hydrocephalus there is a severe, persistent inflammatory process with destruction of the ependyma. He assumed that in the absence of obstruction thorotrast disappears from the ventricular system within four days, but he did not present clearcut evidence to support this view. He added further that in patients with obstruction the choroid plexus was restored to a normal condition within four days after the injection.

Radovici, Bazgan and Meller [6] and Jacobi, Löhr and Wustmann [3b] reported changes caused by thorotrast injected into the ventricles and emphasized especially a macrophagic reaction, destruction of the ependymal lining and the freedom of the brain tissue from parenchymatous alterations.

Reeves and Stuck,[7] on the other hand, in a general review of the subject concluded that the dangers involved in the use of this substance outweighed the possible advantages. They carried out thorough roentgen and histologic studies on the behavior of thorotrast in monkeys and reached the conclusion that "no consequential transportation of the substance from the subarachnoid spaces into the blood stream occurs." They discussed the radioactivity of thorotrast, which they felt was an important contraindication to its use and a likely factor in the injurious effect. In a later paper [8] they described the development of hydrocephalus after injection of thorotrast in cats, dogs and monkeys.

Alexander, Jung and Lyman,[9] working with dogs, found damaged ependyma and alterations which they regarded as evidence of the ependymal origin of the macrophages involved in the reaction to thorotrast.

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5. Freeman, W.: Arch. Neurol. & Psychiat. **38**:340, 1937.
6. Radovici, A.; Bazgan, I., and Meller, O.: Encéphale **28**:726, 1933.
7. Reeves, D. L., and Stuck, R. M.: Medicine **17**:37, 1938.
8. Stuck, R. M., and Reeves, D. L.: Arch. Neurol. & Psychiat. **40**:86, 1938.
9. Alexander, L. T.; Jung, S., and Lyman, R. S.: Arch. Neurol. & Psychiat. **32**:1143, 1934.

It is obvious from the foregoing citations that the question as to whether the use of thorotrast in human beings is entirely without hazards is not fully answered, and therefore it is thought advisable to record all reliable observations bearing on this problem. The case which will now be reported is of value because of a detailed histologic study made on the brain a month after the introduction of thorotrast by ventricular puncture.

REPORT OF A CASE

A 5 year old girl was brought to the hospital Feb. 24, 1936. Two weeks after an apparently normal birth, stiffness of her left arm was observed. The stiffness did not persist but occasionally recurred in attacks of convulsions with cyanosis. At six weeks she experienced several attacks of generalized convulsions with cyanosis. By the age of 3 months the seizures had stopped. Development then seemed to proceed normally—the child sat up at 6 months, stood at 10 months, walked at 14 months and talked at 18 months. When she began to walk, it was noted that she dragged her left leg. At the age of 2 years, she was struck on the head by a dropping toilet seat. She showed no marks of local injury, but ten minutes later, while being fed, she suddenly vomited, became unconscious and was seized by a severe generalized convulsion. She was taken to a hospital where a general anesthetic was required to control the convulsion. She regained consciousness several hours later. A roentgen examination of the skull revealed no fracture. Following this episode, the child became subject to convulsive seizures with or without preceding nausea or vomiting. The attacks recurred at intervals of several months and were usually associated with infections of the upper respiratory tract. At the age of 3 years (in April 1933), during the course of an acute illness with fever and a rash (the exact diagnosis could not be ascertained), she passed through a severe seizure, with her temperature rising to 108 F. At the age of 4½ years, during another severe seizure, with her temperature rising to 105 F., a spinal tap yielded bloody fluid. She remained unconscious for several days, the left leg being held in flexion. She then continued in a semicomatous state for ten days. As she was regaining consciousness, it was noted that she spoke in a parrot-like fashion and was unable to form complete sentences. She had become easily frightened and was difficult to manage.

The child was well nourished. She did not respond to simple commands and did not display any emotional reaction. The left palpebral fissure was wider, and the left pupil larger, than that on the right. The fundi were normal. There were paresis of the central type of the left side of the face and spastic paralysis of the left arm and leg. All deep reflexes were increased, and the abdominal reflexes were diminished on the left side. There was a Babinski sign on the left.

The cerebrospinal fluid at the time of admission was normal. The Wassermann tests of the blood and spinal fluid were negative.

On admission an injury sustained at birth and a developmental defect of the right prefrontal area were considered as diagnoses, with some vascular anomaly or a porencephalic defect also being suggested as possibilities. Four days after admission encephalographic examination revealed marked internal hydrocephalus, the right ventricle being larger than the left. The third ventricle was distended. This examination was not altogether satisfactory and March 15 ventriculographic examination was again made and showed marked internal hydrocephalus. Following this procedure the child experienced numerous convulsive seizures, and slight

papilledema appeared in the right disk. As the papilledema advanced and became bilateral a midline tumor was accepted as a likely diagnosis, particularly since, on March 24, ptosis of the left lid and paresis of the upper and outward movement of the left eye developed.

On March 27 a ventriculographic examination was made with the use of thorotrast. It disclosed huge lateral ventricles but no trace of the third ventricle. The next day, March 28, four weeks after admission, a suboccipital craniotomy was performed. When the cisterna magna was opened, the foramen of Magendie

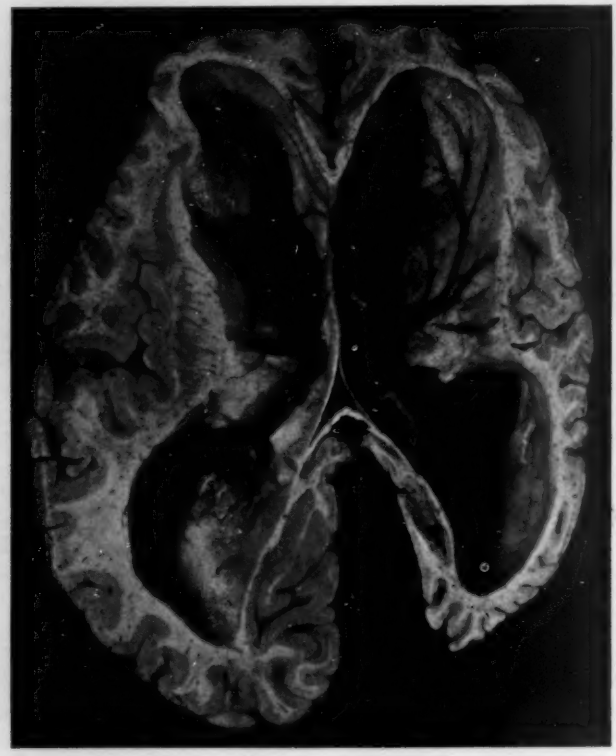

Fig. 1.—The gross appearance of the brain, showing hydrocephalus with atrophy of the right hemisphere.

was found to measure 0.5 cm. in diameter. The fourth ventricle was also enlarged. A fragment of pia-arachnoid from the cisterna magna was removed for histologic study. This showed chronic reactive leptomeningitis secondary to "subarachnoid hemorrhage." Following the operation the patient's condition became progressively worse. The spinal fluid, which had been clear on repeated examinations, became cloudy twenty-five days after operation. The temperature rose to 105.2 F. Violent convulsive seizures set in, during which the child assumed a posture of decerebrate rigidity. She died during one of these seizures, on April 23, eight weeks after admission and four weeks after operation following ventriculographic examination by means of thorotrast.

Postmortem Examination of Brain.—The right cerebral hemisphere was smaller in all respects than the left. On sectioning, the enlargement of the ventricles was brought to view, the smaller right hemisphere having the larger ventricle (fig. 1). The foramina of Monro were markedly dilated; the aqueduct of Sylvius and the fourth ventricle were also dilated but to a lesser degree. The cerebellum appeared normal.

Microscopic Examination of Brain.—The architecture of the cerebral cortex was markedly disturbed. This was due to a reduction in the number of nerve cells and subcortical fibers and to a relative increase in glial elements. The gliosis

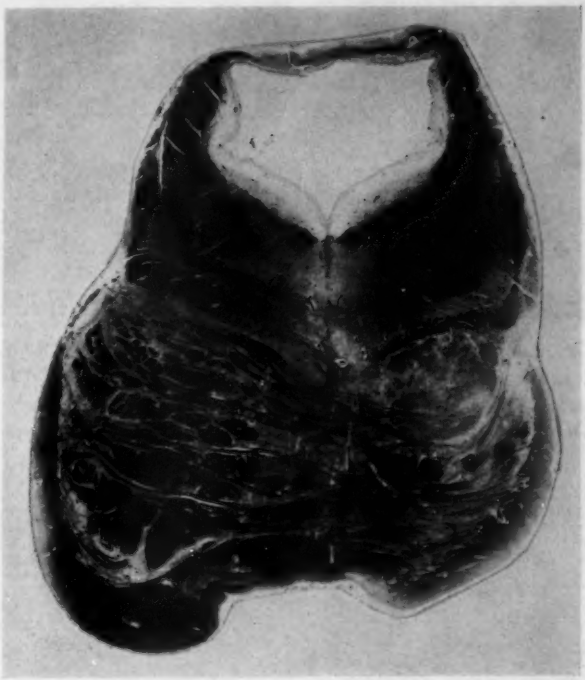

Fig. 2.—Section of the pons showing almost complete disappearance of the fibers of the pyramidal tract on the right side.

affected all glial elements. In some sections the gliosis appeared most marked in specific layers of the cortex. The deeper layers of the cortex were disorganized, owing to extensive loss of cellular elements. These changes were present in both hemispheres but most marked in the right.

Scarlet red stains showed small deposits of fat scattered throughout the cortex and subcortex but concentrated chiefly about blood vessels. The subependymal zone was free from fat.

Sections of the midbrain, pons and medulla oblongata revealed marked reduction in the volume of the fibers of the pyramidal tract on the right side (fig. 2). In addition, stellate foci of demyelination were found in the pes pedunculi on each side.

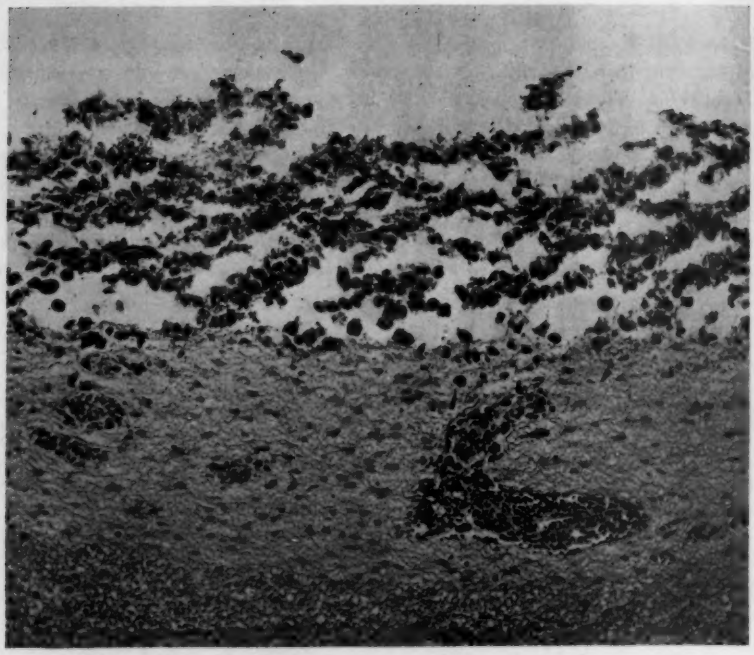

Fig. 3.—Section displaying the ventricular lining of the posterior horn of the right lateral ventricle. It is almost completely desquamated, and the ependymal cells are rounded up to form macrophages, which contain thorotrast.

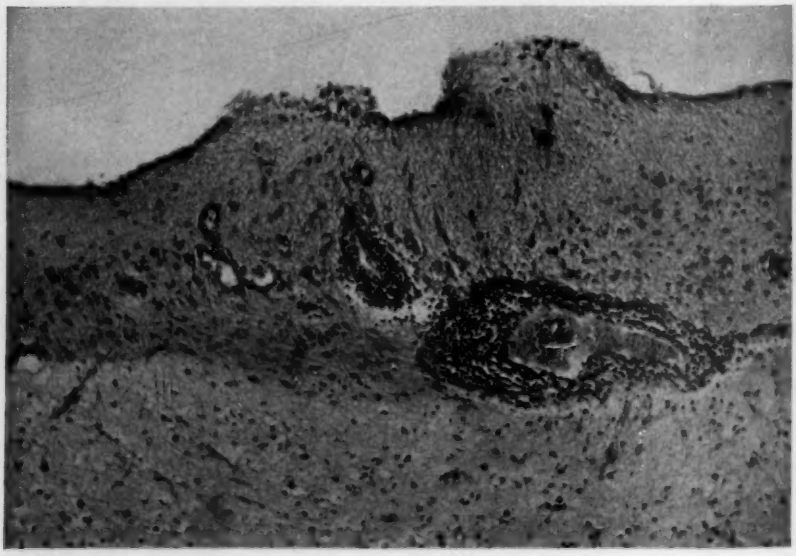

Fig. 4.—Section of the ventricular lining showing ependymal granulations and perivascular infiltration in the subependymal zone.

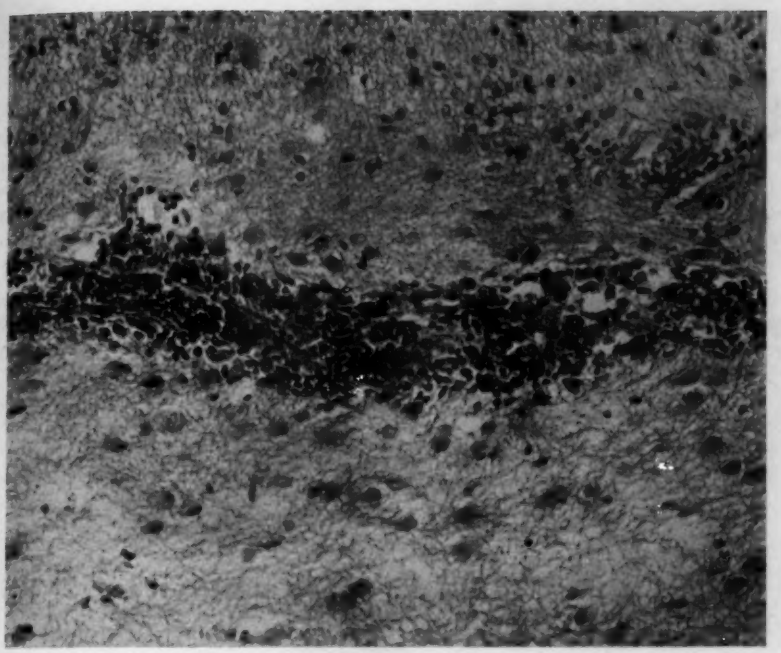

Fig. 5.—Macrophages, containing granules of thorotrast, enveloping a large vessel in the subependyma.

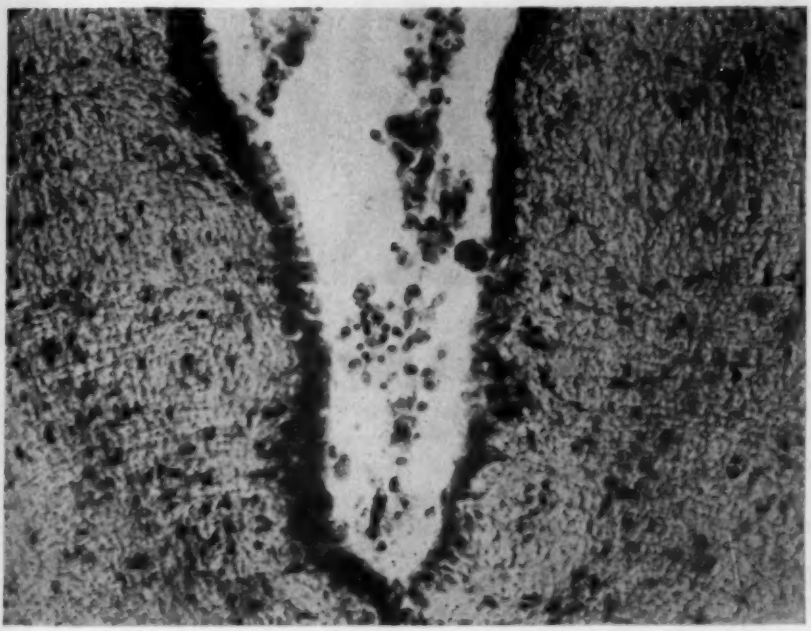

Fig. 6.—Section of the midbrain showing part of the aqueduct of Sylvius with intact ependymal lining and thorotrast-containing macrophages free in the aqueduct.

The ependymal cells were swollen and vacuolated, some containing granules of thorotrast. The underlying supporting tissue was densely infiltrated by macrophages containing particles of thorotrast. At one site there was a large accumulation of macrophages about blood vessels. Covering the ependyma were large aggregates of thorotrast-laden macrophages. The ependymal lining for the most part, however, remained intact, presenting a sharp contrast to the surrounding masses of macrophages on the surface and in the subependymal connective tissue.

In the right lateral ventricle the ependymal lining was almost entirely desquamated (fig. 3). Lying free in the ventricular cavity were large numbers of macrophages containing granules of thorotrast. Ependymal granulations occurred

Fig. 7.—Preparation showing ependymal cells in the process of desquamation.

at frequent intervals (fig. 4). The subependymal blood vessels showed a striking perivascular infiltrate of thorotrast-laden macrophages and lymphocytes. This reaction was usually found near an area of severely damaged ependyma (figs. 3, 4 and 5).

The ependymal lining in the left lateral ventricle and in the third ventricle showed milder forms of the same pathologic process. In the aqueduct of Sylvius the ependymal lining was intact except for scattered foci of injury. There were, however, accumulations of macrophages resting on the intact ependyma (fig. 6).

At several points there appeared thorotrast-containing cells suggestive of desquamating ependyma cells (fig. 7).

The pia-arachnoid showed varying changes at different sites. The interpeduncular space was crowded with a large quantity of thorotrast-laden macrophages. Scattered macrophages were found in the subarachnoid spaces over the convexity of the brain and surrounding the spinal cord.

Macrophages did not appear in the pacchionian bodies or in the dural sinuses.

SUMMARY

In the case herein described the patient lived for twenty-seven days after the introduction of thorotrast into the ventricular system. A large amount of this substance was still present in the ventricular cavities and in the subarachnoid spaces, though there was no obstruction to the flow of cerebrospinal fluid, as demonstrated by the fact that a considerable accumulation of thorotrast-laden macrophages was observed in the subarachnoid spaces.

The observation of particles of thorotrast in macrophages is at variance with the assumption made by Freeman that in the absence of obstruction the substance disappears from the ventricular cavities within four days. It is, however, in accord with the evidence presented by Radovici and Meller,[2e] Stuck and Reeves [8] and Jacobi and his co-workers.[3b]

The thorotrast caused extensive damage in the ependymal lining, especially in the right lateral ventricle, into which the substance had been directly introduced. The pathologic changes consisted of desquamations of ependymal lining and extensive macrophagic accumulations in the ventricular cavities, about the choroid plexus and in the subarachnoid spaces. Thorotrast-laden macrophages were also found in the perivascular spaces of the subependymal zone. In several areas ependymal cells filled with particles of thorotrast could be seen becoming detached and rounding up (fig. 7). This points to the ependymal cells as the probable source of origin of the macrophages, an observation which is in accord with the views of Alexander, Jung and Lyman.[9]

CONCLUSIONS

Thorotrast (colloidal thorium dioxide) is not readily excreted by the central nervous system and may remain in the ventricular cavity for long periods (in this case, for twenty-seven days) in spite of the absence of obstruction to the flow of the cerebrospinal fluid.

Thorotrast produces extensive inflammatory and destructive changes in the ependymal lining. The source of the macrophages which ingest the granules of thorotrast may be traced in part at least to ependymal cells.

The use of thorotrast in patients for the visualization of ventricular cavities is unsafe.

Case Reports

HODGKIN'S DISEASE WITH INVASION OF PERICARDIUM AND GALLBLADDER

Review of the Literature and Report of a Case with Autopsy

GEORGE T. HARRELL, M.D., DURHAM, N. C.

Since the original description by Hodgkin of the disease which now bears his name, a vast literature has accumulated. Although the etiologic factors are still unknown, the definite criteria which have been established for making the diagnosis would probably exclude many of the cases earlier reported to be instances of this disease. Although the lesions are found primarily in lymphoid tissue, various writers have described lesions of Hodgkin's disease in practically every organ in the body. Since lesions of the pericardium and of the biliary tract are among the rarest, it was thought that the case to be reported now warranted recording, and that a review of the literature on these lesions would be interesting.

LITERATURE

Reed [1] reported a case of Hodgkin's disease in which several nodular lesions with the typical microscopic appearance were found in the pleuropericardial membrane. Yamasaki [2] reported a "sarcoma of the thymus" breaking through the parietal pericardium at numerous places. Microscopically the tumor had polymorphous characteristics consistent with the lesions of Hodgkin's disease. Karsner [3] agreed with Yamasaki in the belief that Hodgkin's tissue can be transformed into malignant polymorphus cell sarcoma, and he so classifies the condition observed by Yamasaki. Meyer [4] reported a growth invading the pericardium which grossly resembled lymphosarcoma. Though no mention is made of pericardial sections, the adjacent lymph nodes microscopically showed "malignant granuloma"; the cellular description is consistent with that in the preceding case. Yates and Bunting [5] mentioned an acute condition macroscopically resembling a malignant tumor with many nodular lesions in the visceral pericardium and "typical Hodgkin's granulomatous infiltration microscopically." Other cases reported in the older literature and cited in extensive reviews of Hodgkin's disease are questionable either because of the lack of microscopic descriptions or because the histologic descriptions indicate that they are probably not instances of Hodgkin's disease.

From the Department of Pathology, Duke University School of Medicine.

1. Reed, D.: Johns Hopkins Hosp. Rep. **10**:133, 1902.

2. Yamasaki, M.: Ztschr. f. Heilk. **25**:269, 1904.

3. Karsner, H. T.: Arch. Int. Med. **6**:175, 1910.

4. Meyer, O.: Frankfurt. Ztschr. f. Path. **8**:343, 1911.

5. Yates, J. L., and Bunting, C. H.: J. A. M. A. **64**:1953, 1915.

More recently Terplan and Mittlebach [6] described lymphogranulomatous infiltration of the pericardium with "concretio cordis cum pericardio" in their case 2. In their case 10 they found granulomatous nodules in the epicardium over the right and left ventricles, and a mass, 6 by 4 by 2 cm., in the epicardium encircling the origin of the great vessels. Their microscopic descriptions do not include pericardial sections but only typical lesions in cervical lymph glands. The lesion in case 2 is illustrated.

Rimbaud [7] described a case in which there was extensive invasion of the subepicardial tissues and of the parietal pericardium. Dalous, Fabre and Pons [8] reported a gelatinous infiltration over the ventricles at the exit of the great vessels with involvement of the parietal pericardium. The descriptions of the latter 2 cases and the photomicrographs of the lesions leave no doubt of the diagnosis of Hodgkin's disease. Of these 8 cases, the last 3 alone present a degree of involvement comparable to that in the present case.

Meyer [4] reported invasion of the common bile duct by a "tumor" microscopically consistent with Hodgkin's tissue; the gallbladder was not involved. Stahr and Synwoldt [9] reported Hodgkin's tissue in the common and cystic ducts with compression of the lumens; two lymph nodes at the neck of the gallbladder showed typical microscopic lesions. The gallbladder was soft, filled with bile and apparently normal. No other instances of involvement of the biliary tract apart from compression of the ducts by enlarged lymph nodes were found.

REPORT OF CASE

A 35 year old white man, a farmer and married, was admitted to Duke Hospital, June 17, 1935, complaining of pain in the left side of the chest and swelling in the neck, present for six weeks.

The family, marital and past histories of the patient were noncontributory.

About six weeks before admission, a sharp pain suddenly developed in the left shoulder and spread along the clavicle to the anterior part of the neck and sternum. After several days a painful red swelling appeared in the left cervical region. The patient was totally incapacitated from the outset, with high sustained fever, weakness, night sweats and an indefinite loss of weight. Tachycardia and edema of the hands, face and feet developed.

On admission the patient was acutely ill, with a temperature of 39 C. (102.2 F.), a pulse rate of 120, a respiratory rate of 22 and blood pressure of 112 systolic and 55 diastolic. The right pupil was larger than the left; the tonsils were moderately enlarged and infected, and the left was larger than the right.

A smooth red edematous swelling of the lower two thirds of the left anterolateral aspect of the neck extended down to involve the wall of the chest and obliterated the paraclavicular and episternal fossae. It was indurated and not tender.

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6. Terplan, K., and Mittlebach, M.: Virchows Arch. f. path. Anat. **271**: 759, 1929.

7. Rimbaud, P.: Ann. d'anat. path. **11**:43, 1934.

8. Dalous; Fabre, J., and Pons, H.: Arch. d. mal. du cœur **29**:89, 1936.

9. Stahr, H., and Synwoldt, I.: Med. Klin. **1**:404, 1922.

The axillary lymph nodes were enlarged, firm and discrete, with the largest, on the left side, measuring 4 by 6 cm. A tender left submaxillary node was the only other palpable node. The left upper anterior thoracic wall was prominent, and signs of consolidation were noted. The heart did not appear to be enlarged. The sounds were faint, and there was a pericardial friction rub. The other physical findings were negative. No jaundice was present.

The hemoglobin content was 12.3 Gm. (Sahli); the red blood cell count, 3,650,000; the white blood cell count, 11,800, with 81 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 9 per cent small lymphocytes, 16 per cent large lymphocytes and 3 per cent monocytes. The results of examinations of the urine, stool and sputum, the Wassermann and Kahn reactions and the blood culture were negative. An electrocardiogram showed only sinus tachycardia. Fluoroscopic and roentgen examination of the chest showed diffuse infiltration of the upper lobe of the left lung and a very small amount of fluid at the costophrenic angle. The heart was large and rounded, and the pulsations were feeble. A diagnosis of Hodgkin's disease was made from sections of a lymph node removed from the left axilla.

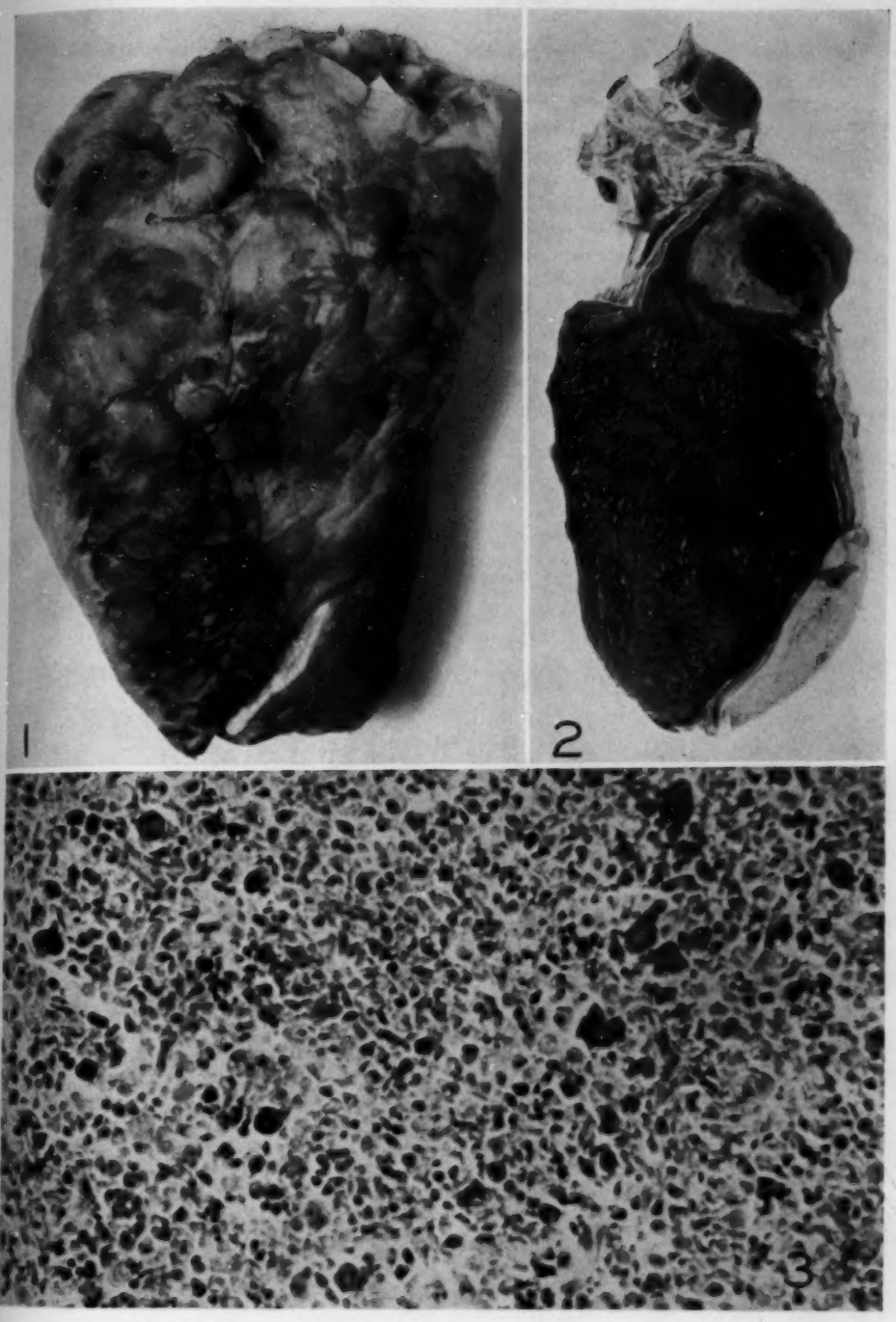
The fever continued, with the temperature ranging between 39 and 40 C. (102.2 and 104 F.), showing small daily fluctuations, and there was a correspondingly high pulse rate. The white blood cell count ranged from 12,000 to 21,000, averaging about 90 per cent polymorphonuclear neutrophils. The hemoglobin content rapidly fell to 6.5 Gm. The patient began to produce some bloody sputum, which was negative for acid-fast and other organisms. He received roentgen therapy, consisting of 130 to 200 roentgens applied over the left upper part of the chest and neck, four times at two day intervals, with little change in the roentgen or physical findings. He died in coma approximately nine weeks after the onset.

Postmortem Observations.—The anatomic diagnosis was: fulminating Hodgkin's disease, with invasion of mediastinal, cervical, axillary and retroperitoneal lymph nodes and of the left sternocleidomastoid muscle, pericardium, epicardium, myocardium, spleen, left lung, diaphragm, thyroid, gallbladder, mediastinum and trachea; focal necrosis in the spleen, left lung and lymph nodes; fibrinous pericarditis and pleurisy, with fibrous pleural adhesions; adenoma of the thyroid; fibrosis of the testis.

An autopsy was made five hours after death. When the thorax was opened, there was encountered a pale nodular mediastinal mass, firm in consistency and 8 cm. in diameter. At the point where the aorta issued from the pericardium there was a layer of soft, almost fluctuant, white material, 2.5 cm. thick. The pericardium was 8 mm. thick and contained 125 cc. of thin bloody fluid; it presented the picture of fibrinous pericarditis. The entire serous surface was covered with shaggy pale translucent nodules, firm to the touch, the largest being 2 cm. in diameter.

The heart weighed 300 Gm. A layer of bright yellow fat with a maximum thickness of 4 mm. lay between the greatly thickened epicardium and the myocardium. It was more prominent over the right ventricle (fig. 1).

The pleural surfaces were bound together with fine, easily broken fibrous adhesions except over the left apex, where the surfaces were densely adherent. There was no free pleural fluid. The left lung weighed 730 Gm.; the upper lobe was firm, rubbery and uniformly pale gray. The lymph nodes at the hilus were large and soft and contained many gray granular areas. The right lung was normal and weighed 500 Gm. The entire mucosa of the trachea, beginning very sharply 6 cm. below the vocal cords, was infiltrated with a soft reddish growth, granular and friable, which partially obstructed the lumen of the right major bronchus.



1, heart, anterior surface. *2*, gallbladder in cross section. *3*, tissue from cervical region involved in Hodgkin's disease; Dominici stain; × 200.

About 100 cc. of necrotic material resembling thin pus came from the left side of the neck; smears revealed no polymorphonuclear leukocytes or organisms. A great mass of soft, friable, necrotic lymphoid tissue in the cervical region somewhat resembled caseous tuberculous tissue. The sternocleidomastoid muscle was hard and was infiltrated with dense white tissue.

The liver extended 4 cm. below the costal margin and weighed 1,760 Gm. The spleen was enlarged, weighing 220 Gm., and had soft, bulging red pulp. At the junction of the cystic duct with the gallbladder was a 2 cm. mass of firm white tissue, covered with mucosa on one side and peritoneum on the other; the duct was not obstructed (fig. 2). The mesentery contained numerous rubbery nodes up to 1.5 cm. in diameter.

The entire abdominal aorta and the common iliac arteries were surrounded by a mass of firm nodes, averaging 2 cm. in length, which did not constrict the lumens. The other organs showed nothing of importance. The brain and spinal cord were not examined because permission to do so was refused.

Cultures of the spleen and of the purulent material from the neck revealed no pathogenic organisms. (Since this paper was prepared, cultures of Brucella have been recovered in this laboratory from material from 4 patients clinically and pathologically presenting the picture of Hodgkin's disease.[10] In the present case cultures were not made specifically for that organism.)

Tissues were fixed in Zenker's fluid containing solution of formaldehyde U. S. P. instead of acetic acid (Helly's modification) and in solution of formaldehyde U. S. P., diluted 1:10. Sections were stained with hematoxylin-eosin, Van Gieson, Masson, Mallory, Heidenhain, Pappenheim, Dominici,[11] Giemsa, Kingoun acid-fast[12] and MacCallum bacterial[13] stains.

The axillary lymph node removed twelve days before death and preceding roentgen therapy revealed fibrosis, hyperplasia and focal necrosis. Eosinophils were rare; Dorothy Reed cells were numerous. The multinucleated cells were most prominent in the sinuses just under the capsule.

The tissue showing Hodgkin's disease obtained at autopsy was uniformly made up of three main types of cells (fig. 3): (1) giant cells with a maximum diameter of 40 microns, irregularly shaped, with from two to eight large vesicular nuclei, which were often arranged around the periphery, occupying most of the cell; (2) smaller rounded cells with a maximum diameter of 20 microns, with a single nucleus of denser character and a wide border of deep-staining cytoplasm; (3) lymphocytes and a few plasma cells. No eosinophils were found. The mitoses, which numbered two to six per high power field, were found principally in the

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10. Parsons, P. B., and Poston, M. A.: South. M. J. **32**:7, 1939.

11. The Dominici method is as follows: Stain with eosin–orange G (0.5 Gm. in 100 cc. of distilled water) and counterstain with a 0.5 per cent aqueous toluidine blue.

12. The Kingoun method makes use of a stain prepared as follows: Boric fuchsin, 4 Gm.; phenol crystals, 8 Gm.; 95 per cent alcohol, 20 cc., and water, 100 cc. Counterstaining is done with Löffler's methylene blue solution.

13. The MacCallum method is as follows: 1. Apply the Goodpasture stain (basic fuchsin, 0.59 Gm.; aniline oil, 1 cc.; phenol crystals, 1 cc., and 30 per cent alcohol, 100 cc.). 2. Differentiate in solution of formaldehyde U. S. P. (40 per cent). 3. Counterstain with saturated aqueous trinitrophenol. 4. Stain with Sterling's gentian violet. 5. Stain with Gram's iodine. 6. Clear in aniline oil and xylene.

large mononuclear cells. Considerable necrosis with little fibrosis was present. Blood vessels and lymphatics in all sections contained these cells.

A dense zone of Hodgkin's tissue, having a thin layer of fibrin on the edge next to the pericardial cavity, extended into the pericardium, epicardium and myocardium. The tissue invaded the muscularis and the folds of the mucosa in the gallbladder, the muscle bundles in the sternocleidomastoid muscle and in the diaphragm, the alveoli of the lung, the mucosa of the trachea and the capsule of the thyroid. Invasion of the spleen was slight, but necroses were prominent. No invasion of the liver or bone marrow—femur, rib vertebra—was found. The femoral marrow was hyperplastic with many eosinophils in all stages of development; the red cell series and the supporting tissue were increased. At several places in the intestines the submucosa was extensively infiltrated with lymphocytes, but no multinucleated cells were seen; the mucosa was intact.

No organisms were found with acid-fast or bacterial stains.

COMMENT

The clinical course in the present case was strikingly similar to that of an acute infection. The pathologic observations suggest that the tissue involved in the disease had taken on malignant, invasive characteristics. This observation has been recorded previously in the literature.

Lesions in the mediastinal lymph nodes are frequently found in postmortem examinations, but the explanation of the rare involvement of the pericardium is obscure. In most of the cases reviewed in this article, lesions in the adjacent lymphoid tissue have extended directly into the pericardium. Since appreciable quantities of lymphoid tissue which might act as primary or secondary foci for the spread of the lesions were not found distal to the anterior mediastinal or intertracheobronchial nodes, one must assume that cells reached the pericardial membrane by retrograde extension through the lymphatics, or that they entered by way of the blood.

There is said to be over the ventricles a rich subepicardial plexus of lymphatics communicating with those of the myocardium and fusing to form two trunks parallel to the coronary arteries.[14] A small preaortic gland may be present as a way station in the course of the right duct, which joins the anterior mediastinal chain. Small laterotracheal and dorsopulmonary glands may interrupt the flow in the left trunk from the ventricle to the intertracheobronchial group. The auricles drain directly into these large groups of glands or into paraphrenic glands as a way station. Valves are rare in the lymphatics of the auricles and are most numerous in the trunks of the ventricles on the anterior surface.

The parietal pericardium drains either directly or through the paraphrenic glands into the right and left anterior mediastinal groups along with lymphatics from the thymus. On the right, an ascending trunk from this group empties into the subclavian or into the jugular vein. On the left, the group drains through the preaortic-carotid trunk into the thoracic duct. Some afferents go through the posterior mediastinal nodes into the intertracheobronchial group, which in turn empties into

14. Rouvière, H.: Anatomie des lymphatiques de l'homme, Paris, Masson & Cie, 1932.

the thoracic duct through the paratracheal nodes. Any of the routes outlined could serve for the spread of lesions from the mediastinal nodes to the pericardium.

The lymphatics of the gallbladder are superficial to the blood vessels and anastomose with those of the liver. The lymphatics of the right side of the gallbladder drain to the lymph gland at the foramen of Winslow, which in turn sends efferents to the preaortic glands, the lateral right aortic glands, those near the superior mesenteric artery and thence into the thoracic duct. The lymphatics of the left side and inferior surface drain into the cystic gland, which is located in the curve of the neck of the gallbladder at its junction with the cystic duct. Efferents from this gland go to the gland at the foramen of Winslow and to the superior retroduodenal pancreatic group. The lymphatic drainage of the cystic and hepatic ducts is shared by both of the aforementioned glands; the common duct drains to the latter. The superior retroduodenal pancreatic and posterior duodenal pancreatic groups receive some afferents from the hepatic and common ducts, respectively. Extension along the anastomotic circulation outlined is the probable route of involvement of the biliary tract in the 2 cases reviewed.[15] Several other instances of lesions of Hodgkin's disease in the cystic gland without involvement of the biliary tract have been reported. No record has been found of extension from this node into the gallbladder. Why this gland and nearby lymphatics are not more frequently involved, or why lesions in the liver, which are relatively common, do not extend directly into the gallbladder, is not known.

SUMMARY

Eight cases of Hodgkin's disease in which pericardial lesions were proved to have occurred are reviewed, and another is reported.

Two cases of this disease in which lesions in the extrahepatic biliary tract were demonstrated are reviewed. The present case is probably unique in the invasion of the gallbladder itself.

15. Meyer.[4] Stahr and Synwoldt.[9]

CHANGES IN THE INTERSTITIAL CELLS OF THE TESTES IN GULL'S DISEASE

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In spite of the relatively enormous literature on the pathologic aspects of myxedema in adults there are only a few specific references to changes in the gonads, although the striking difference in the sex incidence of the disease and the usual onset during the decline of active sexual life in patients of both sexes have been fully appreciated by all contributors.

The more important symptoms referable to the male gonads are impotency, loss of sexual desire, decrease in the size of the testes and enlargement of the breasts.

I have been unable to find any references to microscopic studies of the testes in Gull's disease, and on this account the following report of a case may be of interest.

REPORT OF A CASE

P. G., aged 63, was admitted to Montefiore Hospital Dec. 4, 1933, and died Sept. 17, 1934. His chief complaints were gradual loss of energy, diminution of muscle strength, increased sensitivity to cold and changes in speech and facies, over a period of five years. For the past six months he had had precordial pain.

The man was well nourished. He had acromegaloid features, slow, coarse speech and prominent lips and nose. His tongue was not enlarged. The upper and lower eyelids were puffy. The fundi were normal. The chest disclosed moderate emphysema. The lungs were clear.

Six months after admission the patient presented alternating diarrhea and constipation. Proctoscopic examination revealed carcinoma of the rectum. The tumor progressed rapidly and within two months invaded the bladder, causing cystitis and ascending infection of the kidneys.

Basal metabolism tests showed a rate of —18 per cent three days after admission and a rate of —29 per cent three weeks later. During the nine months of observation the rate fell to this level twice again, when the administration of desiccated thyroid was discontinued. The red blood cell count was 4,100,000; the white cell count, 11,700; the hemoglobin content, 90 per cent. The Wassermann test was negative. A chemical study of the blood showed sugar, 84 mg. per hundred cubic centimeters; urea, 10.9 mg.; calcium, 10 mg.; phosphorus, 3.7 mg.; cholesterol, 207 mg. Gastric analysis showed the presence of free hydrochloric acid.

Necropsy.—The anatomic diagnosis was: myxedema (clinical), atrophy of the thyroid, carcinoma of the sigmoid flexure, atrophy of the interstitial cells of the testes, chromophobic adenomas of the anterior lobe of the pituitary and generalized atherosclerosis.

From the Laboratory Division, Montefiore Hospital.

The heart weighed 270 Gm. The coronary arteries were sclerotic; there was partial occlusion of the left descending and left circumflex branches but no evidence of infarction. The liver weighed 1,100 Gm., was firm and cut with increased resistance. The left adrenal weighed 6.5 Gm.; the right, 10 Gm. The cortex of each was well developed and of normal color. The medulla was distinct. The gastrointestinal tract was normal save for an irregular, cauliflower-like tumor,

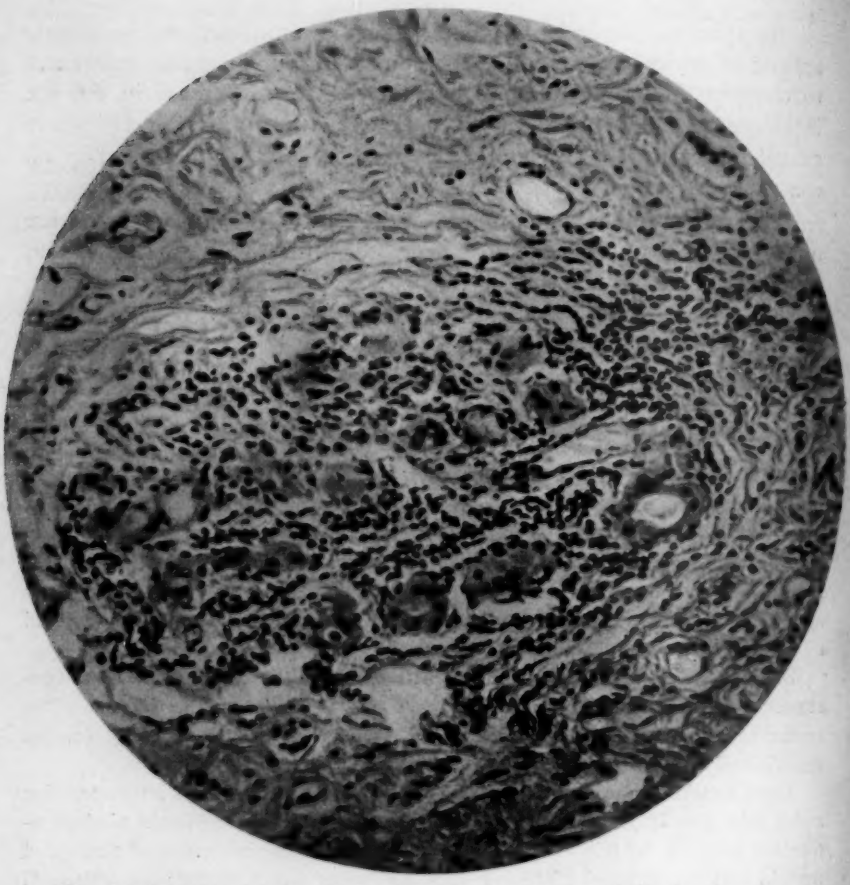

Fig. 1.—Atrophic lobule of the thyroid, showing interfollicular lymphocytic infiltration and exhaustion atrophy of the follicular epithelium.

beginning approximately 17 cm. above and extending to within 5 cm. of the anus. The testes were softer than normal. The right weighed 20 Gm.; the left, 15 Gm.

The lateral lobes of the thyroid were yellowish firm bandlike masses, measuring 3 by 1 by 0.5 cm. The parathyroids appeared normal. The brain weighed 1,220 Gm. No gross abnormalities were noted. The pituitary had a normal outline and weighed 0.679 Gm.

Microscopic Examination.—The thyroid showed generalized increase in connective tissue. The lobules were reduced to small, widely scattered nests of

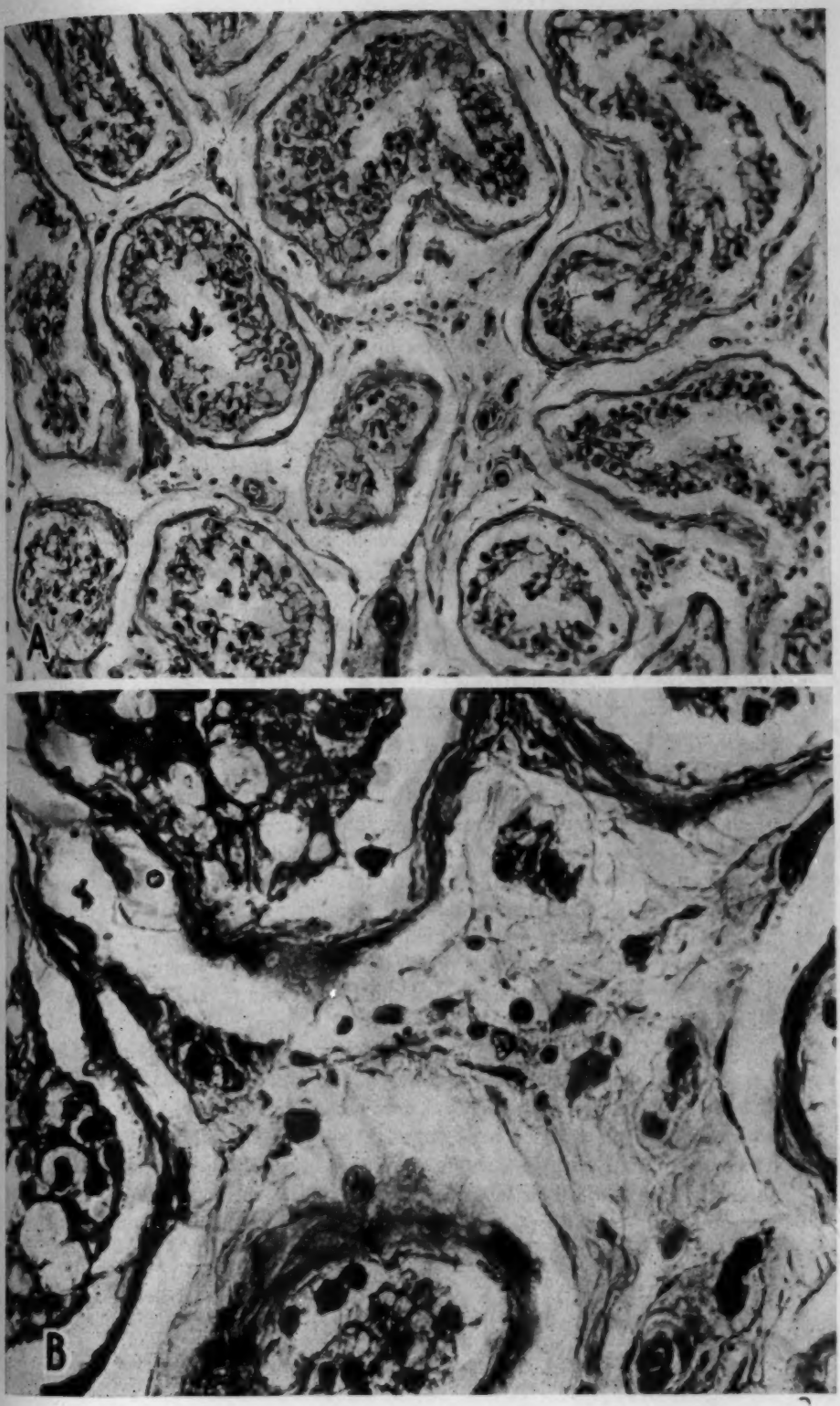

Fig. 2.—*A*, testicular tissue showing absence of spermatogenesis, widening of interstitial spaces, and atrophy and degeneration of interstitial cells; *B*, higher magnification of *A*.

shrunken, distorted follicles, and each lobule was infiltrated by lymphocytes. The epithelial cells of the atrophic follicles were highly irregular in size and shape. Some cells contained large, distorted nuclei; in others the nuclei were small and pyknotic (fig. 1).

The parathyroids were normal.

In the testes the tubules were small and widely separated. Spermatogonia were definitely reduced in number. There was no spermatogenesis. The Sertoli cells were intact. The interstitial spaces were widened, and the interstitial cells were greatly reduced in number and distorted in form. In some the nuclei had been preserved, but most of the cells were in an advanced stage of degeneration and were represented by cytoplasmic fragments or small yellowish or brownish masses of pigment (fig. 2 *A* and *B*).

The pituitary revealed slight basophilic infiltration of the posterior lobe and generalized increase in the stroma of the anterior lobe. One definite and several indefinite chromophobic adenomas were noted. There was an increase in the number of cells taking a diffuse eosin stain (hematoxylin-eosin stain; Orth's fixation). With Mallory's stain, after mordanting in Zenker's fluid, the cells did not show stainable granules.

COMMENT

Atrophy of the testes is referred to occasionally in clinical reports of cases of Gull's disease, but I have been unable to find any reference to microscopic changes in the testes. The only detailed reports possibly related to this subject are of cases of cachexia strumipriva, by Wegelin.[1] In my opinion this condition is not comparable to Gull's disease because thyroidectomy during active sexual life tends to, and often does, increase the activity of the gonads, directly by removing the inhibiting effect of the thyroid hormone on the gonads and indirectly by stimulating the gonadotropic activity of the anterior lobe of the pituitary.[2] The increased sensitivity of the gonads to gonadotropic substances following thyroidectomy is another manifestation of this phenomenon.[3] One of Wegelin's patients was 47 years old and died of heart disease. A fragment of thyroid was found at necropsy. Both testes were below normal size and weight. The tubules were small, but there was definite, although greatly reduced, spermatogenesis. The interstitial spaces were widened and edematous. The interstitial cells were "not increased" and contained only a trace of pigment. Wegelin's second patient was 56 years old and died of heart disease. He had received desiccated thyroid for twenty years, beginning ten years after total thyroidectomy at the age of 16. The testes were small, and the cut surface was brownish. There was active, although greatly reduced, spermatogenesis. The interstitial cells were few and widely scattered and contained fine fat droplets, which were not doubly refractile. The hypophysis weighed 1 Gm.

1. Wegelin, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 362; Virchows Arch. f. path. Anat. **254**:688, 1925.

2. Marine, D., and Rosen, S. H.: Am. J. Physiol. **121**:620, 1938.

3. Schockaert, J.: Compt. rend. Soc. de biol. **108**:431, 1931.

It is well known that in young adult animals thyroidectomy, despite the very low metabolic rate, usualiy does not lead to a clinical complex resembling Gull's disease, but thyroidectomy regularly causes typical cretinism in infantile animals. In recent years somewhat the same phenomenon has been seen following subtotal thyroidectomy for exophthalmic goiter.[4] In some of the cases in which the metabolic rates were very low clinical signs of Gull's disease developed, while in others such signs did not, and it is possible that the different outcome may have been due in part to different levels of gonadal activity (adrenal cortices and gonads).

The significance of depressed function of the gonads in the development of myxedema has frequently been discussed, and clinical evidence has been brought forward by Curschmann,[5] Deusch,[6] Apert [7] and others which suggests that the decline in gonadal functions may be one of the factors underlying the subsequent failure of the thyroid. This view is based largely on clinical studies, because the anatomic changes in the ovary are difficult of interpretation and evaluation. They cannot be separated from the normal menopausal changes. There is clinical evidence, both direct and indirect, that the postmenopausal ovary may still function in such a way as to offer some protection against atrophy of the thyroid. The indirect evidence is that myxedema rarely occurs as a complication of the menopause, and the direct evidence is that cases have been reported in which myxedema developed abruptly after removal of the ovaries even when this occurred five and even ten years after the menopause. Myxedema has also been reported in males after destruction of the testes by gunshot or by tumor. The typical effect of gonadectomy on the thyroid in sexually mature animals is a temporary (one to two weeks) stimulation of the thyroid probably through the pituitary, followed by involution (as indicated by a rise in iodine [I_2], an increase in density of colloid and flattening of the epithelium). True atrophy of the thyroid following gonadectomy has not been recorded. Anatomic changes in the testes are more easily interpreted than such changes in the ovary, and in the case reported here definite changes were observed in both the germinal epithelium and the interstitial cells. Those in the interstitial cells were much more severe—a reversal of the usual senile changes. In patients with exophthalmic goiter the interstitial cells

4. Thompson, W. O., and Thompson, P. K.: J. Clin. Investigation **5**:441, 1928; **6**:347, 1928. Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Am. J. M. Sc. **179**:773, 1930.

5. Curschmann, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **41**:155, 1918.

6. Deusch, G.: München. med. Wchnschr. **66**:589, 1919.

7. Apert: Semaine méd. **28**:71, 1908.

are ordinarily well preserved even when there is advanced atrophy of the germinal epithelium.

SUMMARY

A case of myxedema in a 63 year old man is reported in which advanced atrophy of the thyroid gland and of the interstitial cells of the testes was found. The suggestion is made that the atrophy of the interstitial cells may be etiologically important rather than coincidental.

General Reviews

PROGRESS IN THE STUDY OF THE TYPHOID BACILLUS

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AND

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The introduction of the exact methods of chemistry and physics into the field of microbiology and the adoption of a corresponding mental attitude have borne fruit which make the writing of a review such as this one a much more gratifying task today than it would have been fifteen years ago.

It is our aim to dwell on those researches in which real progress has been made, rather than to be comprehensive. Still it is hoped that the bibliography given in the footnotes to the text is complete enough to serve as a guide to the bypaths of the subject. It includes papers available up to March 31, 1939. [In cases in which numerous publications from the same laboratory are scattered in various journals—for instance, the reports of Boivin's work—reviews published by the authors themselves are listed so as not to encumber the list with still more references.]

There are three different official classifications used for the typhoid bacillus in English speaking countries. One is Bacterium typhosum, used predominantly in England. Bergey's [1] designation Eberthella typhosa is increasingly followed in the United States. The third is Salmonella typhosa, according to the Kauffmann-White [2] scheme, which assigns Eberthella typhosa to an exact place within the Salmonella group.

The Kauffmann-White formula gives the predominant features of the antigenic mosaic of E. typhosa, namely, the somatic antigens, IX and XII, and the flagellar antigens, d in the a phase and j in the β phase. A nonspecific H phase is not known for the typhoid bacillus. In addition to these, the scheme in its most recent shape includes the

From the Lederle Laboratories, Inc.

1. Bergey, D. H.: Bergey's Manual of Determinative Bacteriology, ed. 4, Baltimore, Williams & Wilkins Company, 1934.

2. Kaufmann, F.: Ztschr. f. Hyg. u. Infektionskr. **120**:177, 1937.

Vi antigen. (For the nomenclature of typhoid receptors as used in Japan see Naito, Aoki and Tsuda.[3])

The flagellar, or H, antigen can be dealt with here briefly, as little new work has been done on this subject. It is generally accepted that the H antigen is of proteinic nature, but no further investigations on it have been published. Duncan [4] reported that H antigen is inactivated by $\pm$ 1/640 molar hydrochloric acid in one hour at 50 C. The H antigen can be removed by repeated washing (Detre [5]). Pijper [6] showed that the flagella of the typhoid bacillus appear, on examination of the living organism, to be contorted to one or two tufts.

The opinion is now predominant that the H antibody does not contribute to antibacterial immunity (Grinnell;[7] Mollari, Reedy and Randall [8]). Whether this is true without restriction is not easy to determine. Experiences like those reported by Mudd, Lucké and Strumia [9] and Maltaner [10] seem to indicate that there are some qualities of the H antibody which may play a role in protection.

As to the somatic antigen, Furth and Landsteiner [11] gave conclusive evidence that its immunologic specificity is determined by a carbohydrate-like substance which contains but little nitrogen. The problem of the somatic antigen was approached by Boivin and Mesrobeanu [12] and Raistrick and Topley [13] independently with one member of the Salmonella group, namely, Salmonella aertrycke. Boivin and Mesrobeanu precipitated suspensions of the bacteria with trichloroacetic acid. They obtained a colloidal supernatant fluid. Further purification was achieved by precipitation with acetone, followed by dialysis. These preparations were named by the authors *antigène complet,* because they were able to demonstrate that the substance was fully antigenic. *Antigène complet* is split by acid hydrolysis into a complex carbohydrate and a fraction called by Boivin and Mesrobeanu *lipide.* The latter

3. Naito, T.; Aoki, V., and Tsuda, D.: Ztschr. f. Hyg. u. Infektionskr. **118**: 666, 1936.

4. Duncan, J. T.: Brit. J. Exper. Path. **16**:405, 1935.

5. Detre, L.: J. Infect. Dis. **60**:319, 1937.

6. Pijper, A.: J. Path. & Bact. **47**:1, 1938.

7. Grinnell, F. B.: J. Exper. Med. **54**:577, 1931.

8. Mollari, M.; Reedy, R. J., and Randall, W. A.: J. Trop. Med. **41**:218, 1938.

9. Mudd, S.; Lucké, B., and Strumia, M.: J. Immunol. **24**:493, 1933.

10. Maltaner, F.: J. Immunol. **26**:161, 1934.

11. Furth, G., and Landsteiner, K.: (*a*) J. Exper. Med. **47**:171, 1928; (*b*) **49**:727, 1929.

12. (*a*) Boivin, A., and Mesrobeanu, L.: Rev. d'immunol. **1**:553, 1935; (*b*) **2**:113, 1936; (*c*) **3**:319, 1937; (*d*) **4**:40 and (*e*) 197, 1938; (*f*) Ann. Inst. Pasteur **61**:426, 1938; (*g*) in Comptes rendus du Sixième Congrès de chimie biologique, Lyon, 1938, p. 401. (*h*) Mesrobeanu, L.: Les antigènes glucido-lipidiques des bactéries, Thesis, Strasbourg, 1936.

13. Raistrick, H., and Topley, W. W. C.: Brit. J. Exper. Path. **15**:119, 1934.

contains, according to these authors, fatty acids, appreciable amounts of acetic acid and small amounts of nitrogen, phosphorus and sulfur. The carbohydrate was shown to contain small amounts of nitrogen ($\pm$ 2 to 3 per cent) and up to 40 per cent reducing substances. An *antigène complet,* or *antigène glucidolipidique,* as it is also called, was shown to be present in all smooth forms of the Salmonella group and of the colon, dysentery and proteus groups. *Antigènes complets* were found to give highly specific precipitative reactions with their corresponding anti-O serums. They elicit typical anti-O antibodies when injected into animals. The polysaccharide alone as obtained by hydrolysis is a hapten. The lipid residue is not antigenic, and it does not react in vitro.

Raistrick and Topley [13] obtained, independently from Boivin and Mesrobeanu, what was evidently the same substance by a different method. They subjected washed, dried bacteria to tryptic digestion and isolated the active material by fractional alcoholic precipitation, the main fraction being obtained with 68 per cent alcohol.

Topley, Raistrick, Wilson, Stacey, Challinor and Clark [14] utilized the experience gained with S. aertrycke for isolating the corresponding substance from E. typhi.

More recently Henderson and Morgan [15] obtained very pure preparations of the "complete antigens" by extracting dried bacilli with diethylene glycol in the cold, followed by precipitation with 33 to 50 per cent acetone or 50 to 60 per cent alcohol.

The type specificities of the polysaccharides from Salmonella obtained by this method were demonstrated also by Beckwith and Morgan.[16] Felton and Wakeman [17] proposed a method for precipitating an immunizing antigen which was similar to that for preparing Felton's pneumococcic antigen. Another rather crude fractionation was described by Aoki, Obi and Tanaka.[18]

The work on the somatic antigen done in France and England marks a significant step ahead. Still, one looks forward with eagerness to the results of further purification and analysis. As serologic investigation has shown, species of Salmonella often contain a plurality of somatic antigens—for instance, in E. typhosa are those labeled IX and

14. Topley, W. W. C.; Raistrick, H.; Wilson, J.; Stacey, M.; Challinor, S. W., and Clark, R. O. J.: Lancet **1**:252, 1937.

15. Henderson, D. W., and Morgan, W. T. G.: Brit. J. Exper. Path. **19**:82, 1938.

16. Beckwith, T. D., and Morgan, H. R.: J. Bact. **36**:28, 1938.

17. Felton, L. D., and Wakeman, F. B.: Bull. Johns Hopkins Hosp. **60**:178, 1937.

18. Aoki, Y.; Obi, K., and Tanaka, H.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **90**:162, 1937.

XII in the Kauffmann-White classification. These antigens cannot be separated by relative absorption with factor-specific antiserums (Meyer [19]). It would be important to know whether these antigenic differences are anchored within one molecule or whether *antigènes complets* harbor mixtures. Relations of this kind are known for instance in the form of the Forssman antigen. (For the *antigène complet* of the Shiga bacillus see the recent paper of Meyer.[20]) The only example of a separation of different somatic antigens within a "complete antigen" was disclosed by the work on the Vi antigen.

Before embarking on this subject, we shall relate the history of this antigen. The first description of it is credited to Felix.[21] The trail which led to his finding started with the old observation that typhoid strains when freshly isolated from patients often proved to be inagglutinable. (For an early American observation of this fact, see Gay and Claypole.[22]).

Felix and Pitt [21] found that such inagglutinable strains are more pathogenic for mice than are the agglutinable ones. They immunized rabbits with live cultures of an inagglutinable strain and found a new agglutinin. The antibodies produced by this antigen are of a comparatively low titer. The agglutination is of the granular type.

O and Vi are antigenically strictly different. Agglutinability by Vi antibody is, of course, related simply to the presence or absence of the Vi antigen. On the other hand, the agglutinability of a strain by O antibody is more or less inhibited in the presence of Vi antigen; and full agglutinability is present only in strains devoid of Vi. This phenomenon of inhibition of O agglutination in the presence of Vi antigen explains the old observation referred to. These basic observations were soon confirmed (Dyaschenko; [23] Almon and Stovall [24]).

Because of the relationship of this antigen to pathogenicity in mice and from other considerations, which we shall discuss later on, Felix called it "virulence antigen," a term soon generally abbreviated to "Vi antigen." Felix and Pitt [25] demonstrated the antigen's independence of the presence or absence of O antigen.

Kauffman [26] devised the designation *V-W Formwechsel,* assigning to the Vi form the symbol V and to the O form the symbol W, the intermediate forms being called V-W. Practical as this scheme is, it has not won many adherents in English-speaking countries.

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19. Meyer, K.: Ann. Inst. Pasteur **62**:281, 1939.
20. Meyer, K.: Compt. rend. Soc. de biol. **128**:746, 1938.
21. Felix, A., and Pitt, R. M.: Lancet **2**:186, 1934.
22. Gay, F. P., and Claypole, E. J.: Arch. Int. Med. **12**:671, 1912.
23. Dyaschenko, S. S.: J. Hyg. **36**:108, 1936.
24. Almon, L., and Stovall, W. D.: J. Immunol. **31**:269, 1936.
25. Felix, A., and Pitt, R. M.: J. Hyg. **35**:428, 1935.
26. Kauffmann, F.: Ztschr. f. Hyg. u. Infektionskr. **116**:617, 1935.

A strain containing Vi but not O antigen is rough in all its aspects. On the other hand, a strain may be devoid of Vi antigen and yet be completely smooth (Felix and Pitt [25]). Kauffmann [26] and Scholtens,[27] while confirming Felix' observation, are not inclined to accept a strain as rough in the strict sense if it contains Vi.

Topley and his co-workers,[14] as well as Henderson and Morgan,[15] Combiesco, Combiesco and Soru [28] and Combiesco and Combiesco [29] showed that it is possible to demonstrate chemical differences between the O and the Vi antigen. Vi antigen, in contrast to O antigen, is precipitable by phosphotungstic acid in sulfuric acid, neutral lead acetate, uranium acetate, mercuric acetate and aluminium acetate. Topley [14] and Henderson and Morgan [15] found also that their Vi antigen and O antigen differ in the biuret reaction and in the ninhydrin test. Boivin and Mesrobeanu [30] found differences in the reducing properties of O and Vi. The content of carbon, hydrogen, nitrogen and phosphorus is essentially the same. Combiesco, Combiesco and Soru [28] reported that *antigène complet* prepared from Vi strains is less filtrable through Seitz E. K. filters and that solutions of Vi antigen are more stable than solutions of O antigen.

The Vi antigen is much more labile than the O antigen. Felix, Bhatnagar and Pitt [31] showed that it is unstable at 100 C. According to Felix, Bhatnagar and Pitt, the immunizing quality is reduced by treatment with small amounts of formaldehyde or by moderate heat (65 C.), so that the treatment of animals with such denatured material results in antibodies of poor protective properties. More intensive treatment destroys the antigenic properties entirely. It is interesting to note that formaldehydized Vi antigen which is capable of evoking antibodies in rabbits is ineffective in horses. These rabbit antibodies are, however, of poor protective quality. This observation was confirmed and amplified in a recent paper by Henderson,[32] who found that serums made with extracts from Vi strains by the diethylene glycol method, regardless of their precipitative and agglutinative titers, had poor protective quality and did not give complement fixation against whole bacilli.

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27. Scholtens, R. T.: Zentralbl. f. Bakt. (Abt. 1) **139**:467, 1937.

28. Combiesco, D.; Combiesco, C. P., and Soru, E.: Compt. rend. Soc. de biol. **126**:1081, 1937.

29. Combiesco, D.; Combiesco, C. P.; Dumitresco, N., and Badenski, A.: ibid. **126**:1079, 1937.

30. Boivin, A., and Mesrobeanu, L.: (*a*) Compt. rend. Soc. de biol. **128**:5 and (*b*) 9, 1938; (*c*) Compt. rend. Acad. d. sc. **206**:1416, 1938.

31. Felix, A.; Bhatnagar, S. S., and Pitt, R. M.: Brit. J. Exper. Path. **15**:346, 1934.

32. Henderson, D. W.: Brit. J. Exper. Path. **20**:11, 1939.

The typhoid organisms contain a number of antigenic substances which do not give evidence of their presence in the smooth forms and not always in the rough forms. Furth and Landsteiner [11b] showed that the R form contains a carbohydrate different from that of the S form. This fact was confirmed by White,[33] who demonstrated, in addition to a carbohydrate characteristic for the R form, the following factors:

1. The Q factor, which is extracted from organisms of the Salmonella group by hydrochloric acid in alcoholic solution. It is a true antigen common to the whole Salmonella group.

2. An antigen ascribed to the ρ form which is a hapten. (The ρ form is best described as a "loss" variant of the rough form deprived of the R hapten.) White obtained the determinant antigen by washing the organisms with hot alcohol. The R and ρ forms, moreover, contain another factor common to both.

3. An antigen called the T fraction, which is common to the Salmonella group and which he identified with the P fraction of Furth and Landsteiner.

Malik [34] recently described a "loss" variant of the R form with an antigen of its own; its relation to White's findings remains to be determined. Malik's speculation about the spatial arrangement of these "minor" antigens touches an important problem, about which but little is known.

Henderson [32] also reported two antigenic fractions from rough strains with complicated relations to each other and also to antigenic qualities present in smooth forms. One of these fractions seems to be responsible for a quota common to both O and Vi antiserums. Henderson is well aware of the similarity of these observations with those of White.

O and Vi forms differ in the appearance of their colonies (Craigie and Brandon;[35] Giovanardi;[36] Malik[37]), colonies of Vi strains being less transparent than those of O forms.

The optimal development of Vi antigen depends much on proper temperature and culture medium (Felix and co-workers;[31] Kauffmann;[38] Detre[5]).

Detre[5] contributed a method of selecting V forms out of V-W cultures by adding O antiserums and subculturing from the supernatant fluid, which, of course, contains the nonagglutinable organisms, rich in

33. White, P. B.: J. Path. & Bact. **34**:325, 1931; **35**:77, 1932; **36**:65, 1933.
34. Malik, J.: Compt. rend. Soc. de biol. **129**:802, 1938.
35. Craigie, J., and Brandon, K. F.: Canad. Pub. Health J. **27**:165, 1936.
36. Giovanardi, A.: Zentralbl. f. Bakt. (Abt. 1) **141**:341, 1938.
37. Malek, J.: Compt. rend. Soc. de biol. **129**:785, 1938.
38. Kauffmann, F.: Ztschr. f. Hyg. u. Infektionskr. **117**:778 1936; footnote 26.

Vi. It seems that Vi-containing micro-organisms can be obtained by suitable methods of selection from practically any strain. Both Kauffmann [26] and Detre [5] obtained, for example, Vi forms from the H-901 strains.

Dwarf colonies of E. typhosa were regarded as irregularities for many years. However, Victorisz,[39] in the course of a recent study devoted to these dwarf forms, found reasons to believe that they represent the genotype of the typhoid bacillus, from which S and R forms either with or without Vi antigen develop and to which they eventually revert.

The discussion about a possible transmutation of typhoid bacilli into saphrophytes and vice versa came to an end after Cruickshank [40] refuted the story of the relation between E. typhosa and the chromobacterium called Bacterium typhi flavum.

The question of the subdivision of typhoid bacilli into types according to fermentative reactions has not attracted much attention during recent years. Kristensen [41] found that the fermentation or the lack of fermentation of rhamnose is a constant quality of a given strain. There is relatively little information regarding the biologic importance of differences in fermentative activities. Since Braun and Cahn-Bronner [42] studied the *Verwendungsstoffwechsel* (appropriative metabolism) of typhoid bacillus, this question has not obtained due attention. The few investigations on bacterial metabolism in which typhoid bacilli were involved can be properly appreciated only in connection with the general problems of this kind. For that study we refer to Stephenson's [43] book. Considerable help in the study of the chemistry of the micro-organisms should be obtained through the use of cultural mediums of simple or known chemical composition, apart from the theoretic and practical interest of such mediums in the field of bacterial metabolism. For instance, Gladstone [44] observed that the formation of Vi antigen depends on the presence of dextrose but is independent of the source of nitrogen available to the bacillus.

No true exotoxin has ever been found. That means that culture filtrates from the typhoid bacillus do not contain appreciable amounts of poisonous material. Only if the bacilli are autolyzed or disrupted do toxic components of the bodies go into solution. Such solutions are called endotoxins, a rather unfortunate term, since it tends to divert

39. Victorisz, K.: Zentralbl. f. Bakt. (Abt. 1) **142**:389 and 404, 1938.

40. Cruickshank, J. C.: J. Hyg. **35**:354, 1935.

41. Kristensen, M. L.: J. Hyg. **38**:688, 1938.

42. Braun, H., and Cahn-Bronner, C. E.: Biochem. Ztschr. **131**:226 and 272, 1922.

43. Stephenson, M.: Bacterial Metabolism, ed. 2, New York, Longmans, Green & Co., 1939.

44. Gladstone, G. P.: Brit. J. Exper. Path. **18**:67, 1937.

attention from the perception that the poisonous material cannot properly be called a toxin. One wonders how greatly progress has been delayed by the general acceptance of such terms. As dissolved bacterial material is thought by many to be a favorable material with which to start immunization, methods to achieve disruption with as little damage as possible to the antigenic substances have been described repeatedly during recent years. The old method of repeated alternate freezing and thawing (Luedke [45]) was recommended by Grasset [46] and Zablocki and Morzycki.[47] Grasset [46] found that it is possible to lower the toxicity of this antigen by adding formaldehyde. Just what the effect of formaldehyde is in this case is not clear, as the toxic substance is certainly not of protenic nature. Boivin [48] expressed the opinion that the solution of formaldehyde renders the somatic antigen less soluble, an effect which may account for the lowering of the toxicity in Grasset's *anaendotoxin.*

A very effective way of disrupting micro-organisms is to treat them with supersonic vibrations; this holds true also for typhoid bacilli (Chambers and Flosdorf [49]).

Boivin and Mesrobeanu [12f] found that the *antigène complet* accounts entirely for the toxicity of the bodies of typhoid bacillus. This has since been confirmed by Topley and his co-workers,[14] Spanedda [50] and Henderson and Morgan.[15] Spanedda [51] emphasized the similarity of the pathologic changes in animals killed by the *antigène complet* and the pathologic features of typhoid fever.

Delafield [52] observed that all these somatic antigens produce a hyperglycemic effect. Furthermore, they diminish the oxygen uptake of rabbit brain but not of muscle suspensions (Delafield and Smith [53]).

Dennis and Senekjian [54] reported on the leukocidal effect of typhoid filtrates in rabbit and human blood.

According to our experience, the extreme loss of weight of such animals as survive sublethal doses of the "complete antigen" of typhoid

45. Luedke, H.: Deutsches Arch. f. klin. Med. **98**:395, 1910.

46. Grasset, E.: Compt. rend. Soc. de biol. **115**:1485, 1934.

47. Zablocki, B., and Morzycki, J.: Compt. rend. Soc. de biol. **117**:789, 1934. Morzycki, J., and Zablocki, B.: ibid. **117**:792, 1934.

48. Boivin, A.: Ann. Inst. Pasteur **61**:758, 1938.

49. Chambers, L. A., and Flosdorf, E. W.: Proc. Soc. Exper. Biol. & Med. **34**:631, 1936.

50. Spanedda, A.: Boll. Soc. ital. di biol. sper. **11**:21, 22, 327, 931 and 933, 1936.

51. Spanedda, A.: Boll. Soc. ital. di biol. sper. **12**:143, 1937.

52. Delafield, M. E.: J. Path. & Bact. **35**:53, 1932; Brit. J. Exper. Path. **15**: 130, 1934.

53. Delafield, M. E., and Smith, H. A.: Brit. J. Exper. Path. **17**:379, 1938.

54. Dennis, E. W., and Senekjian, H.: Proc. Soc. Exper. Biol. & Med. **36**: 61, 1937.

reaches truly astounding proportions. In guinea pigs losses of 50 per cent of weight are not uncommon, and the recovery requires many weeks and even months. This recalls the familiar picture in the convalescence from typhoid fever. Further pharmacologic investigation of somatic antigens would be highly desirable.

The toxic effect of the purified somatic antigen can be prevented by active immunization either with whole bacilli or with somatic antigen, and it can be neutralized specifically by the corresponding immune serum. This point was especially studied by Boivin and Mesrobeanu.[12d] According to our experience, the demonstration of exact stoechiometric relations in the neutralizing effect is difficult because neutralization is limited to low multiples of lethal doses by the technical conditions of the experiment.

A precise determination of antigen-antibody relations is possible by means of precipitation at optimal proportions, and also by determination of antibody N (Henderson and Morgan;[15] our own unpublished experiments).

Preparations of "complete antigen" give powerful complement fixation with the corresponding rabbit serums but not with horse serums (unpublished experiments), an experience which parallels that of Zinsser and Parker[55] as regards the behavior of pneumococcic antibody.

There is an important point which requires elucidation. Boivin and Mesrobeanu[12] found that the somatic antigens of all the members of the Salmonella group as well as dysentery, colon and proteus bacilli are toxic to a similar degree and kill under symptoms very similar to those resulting from the administration of somatic antigen of typhoid bacilli.

These observations in animals seem to be in marked contrast to the characteristic picture of typhoid fever in man. However, this specificity is only partially real; the pathologic picture of infection with any of the various members of the Salmonella group, especially paratyphoid A or B is very similar to that of infection with the typhoid bacillus if the clinical features are those of typhoid fever and not of enteritis.

On the other hand, the apparent specificity of enteric infection may be purely a question of differences in the quantity of poisonous material introduced. We know that the typhoid bacillus and Salmonella paratyphi A, B and C can have a quite peculiar invasive power in man, in contrast to other members of the Salmonella group. Micro-organisms capable of existing and multiplying in the body have a greater opportunity to produce a toxic effect than has a transient invader. Therefore, for a deeper understanding of the processes in typhoid fever one should distinguish between the toxic principle and other qualities which enable the bacillus to maintain itself in the body; these qualities we cannot define precisely.

55. Zinsser, H., and Parker, J. T.: J. Exper. Med. **37**:275, 1923.

For the special case of typhoid infection the puzzle became no less intricate by reason of Felix' discovery of the Vi antigen. In order to understand the situation, we must first take inventory of the present knowledge of the Vi antigen. It is known that this antigen is definitely a separate chemical entity. It is known that it is many times less toxic than the somatic antigen (Boivin and Mesrobeanu [30b,c]; Combiesco and Combiesco; [29] Henderson and Morgan [15]).

The Vi antigen is practically always present in strains recently isolated from human sources, a fact which will be discussed in greater detail later on.

Felix originally was induced to connect Vi antigen with "virulence" by the observation that strains containing it were more virulent for mice than those lacking it (confirmed by Kauffmann [56]). But in order to weigh this argument one must keep in mind that this difference between Vi strains and O strains is a rather slight one; whereas an O strain, such as the famous O-901, causes lethal septicemia in white mice in doses of about 200,000,000 organisms, Vi strains will have the same effect in doses of about 50,000,000 organisms.

Felix and Bhatnagar [57] and Kauffmann [26] showed that Vi strains are more resistant against phagocytosis and that Vi antibody is necessary to render opsonification of Vi strains effective. (In the absence of Vi the O antibody is the bearer of the opsonizing qualities, according to Bhatnagar.[58]) The assumption seems not to be unreasonable that Vi strains are able to overcome the 4 to 1 numerical handicap because their multiplication is less inhibited by the defenses of the body.

Moreover, the differences between O and Vi strains disappear (Scholtens; [27] Henderson [59]) if infection of the mice is effected by a small number of organisms, a result which one is now in a position to achieve by the mucin method (see page 81, last paragraph). Our own experiences concur with these observations.

Felix interpreted his experimental results with active and passive immunity as indicating a relation of Vi antigen to virulence. He found that treatment with vaccines made from a Vi strain had a higher immunizing power than O vaccines. This observation was confirmed by Topley and his associates.[14] It was paralleled by the high protective value of Vi antibody against infection with Vi strains. Our own extensive experience leads us to believe that these differences disappear if infection is effected by the mucin method, which allows one to work with high multiples of lethal doses (10,000 to 100,000 and more); there

56. Kauffmann, F.: Ztschr. f. Hyg. u. Infektionskr. **120**:31, 1937.
57. Felix, A., and Bhatnagar, S. S.: Brit. J. Exper. Path. **16**:422, 1935.
58. Bhatnagar, S. S.: Brit. J. Exper. Path. **16**:375, 1935.
59. Henderson, D. W.: Brit. J. Exper. Path. **20**:1, 1939.

is no summation of the protective effect of O and Vi antibody. Boivin [60] and Boivin and Mesrobeanu [61] recently reported the same observation.

Henderson [59] investigated the problem of passive protection in its relation to (*a*) the amount and (*b*) the virulence of the micro-organisms. He concluded that the protection was affected more by the amount than by the virulence of the micro-organisms. Hence the protective action of antityphoid serums seems to resemble more an antitoxic effect than an antiinfective one. Considerations like this suggest the possibility of bringing the differences of observation to a common denominator.

At the present stage of knowledge, it seems to be too early to form a definite opinion about the biologic significance of the Vi antigen and the antibody against it.

It may be permissible to insert here a few words regarding the efforts that have been made to find in other micro-organisms qualities similar to the Vi antigen of the typhoid bacillus. Felix and Pitt [62] expressed the belief that they had found a Vi antigen in S. paratyphi B. However, Kauffmann [63] held that what Felix and Pitt believed to be Vi antigen is in fact the second (V) antigen of S. paratyphi B, which varies greatly in its quantities from strain to strain.

An antigen identical with the Vi antigen of the typhoid bacillus, as far as can be ascertained, was found in several strains of S. paratyphi C by Kauffmann [26] and by Rouchdi.[64] Meyer [65] demonstrated recently that Vi antigen from S. paratyphi C can be absorbed specifically by Vi antiserum in contrast to the other somatic factors (see page 73, last paragraph). How far Pirosky's [66] antigen of Pasteurella avium has biologic resemblance to the Vi antigen remains to be seen. The similarities mentioned by Pirosky are (1) the fact that this antigen is also an additional somatic antigen and (2) that it is precipitable by uranium salts.

We have several times given examples of the considerable help afforded by an improvement in experimentation with the typhoid bacillus. This justifies our dwelling on a matter which is in itself purely technical.

Rake,[67] following the example set by Nungester and his co-workers [68] and Miller [69] with other bacteria, found that the addition of gastric

60. Boivin, A.: Compt. rend. Soc. de biol. **130**:403, 1939.
61. Boivin, A., and Mesrobeanu, L.: Compt. rend. Soc. de biol. **130**:683, 1939.
62. Felix, A., and Pitt, R. M.: Brit. J. Exper. Path. **17**:81, 1936.
63. Kauffmann, F.: Ztschr. f. Hyg. u. Infektionskr. **118**:318, 1936.
64. Rouchdi, M.: Compt. rend. Soc. de biol. **128**:1022, 1938.
65. Meyer, K.: Compt. rend. Soc. de biol. **129**:485, 1938; footnote 19.
66. Pirosky, J.: Compt. rend. Soc. de biol. **127**:98 and 966, 1938.
67. Rake, G.: Proc. Soc. Exper. Biol. & Med. **32**:1523, 1935.
68. Nungester, W. J.; Wolf, A. A., and Jourdonais, L. F.: Proc. Soc. Exper. Biol. & Med. **30**:120, 1932.
69. Miller, C. P.: Proc. Soc. Exper. Biol. & Med. **32**:1136, 1138 and 1140, 1935.

mucin to a suspension of typhoid bacilli enhances the pathogenicity of these micro-organisms to such a degree that very few are sufficient to kill (Fisk;[70] Buttle and others;[71] Henderson and Morgan;[15] Siler[72]). The mechanism of the action of mucin is unknown. Our own experiences show that a relatively high concentration of mucin is required, namely, about 5 per cent; 3 per cent is inadequate, and 1 per cent is practically without effect. We obtained from Dr. K. Meyer[73] the polysaccharide isolated by him from mucin and we ourselves prepared similar sugars from the neutral and the acid fraction of mucin; we found all these preparations inactive. Anderson and Oag[74] arrived at similar results. According to their findings, the protein fraction embraces the enhancing activity. Whatever the case may be, mucin makes the typhoid bacillus fully virulent for the mouse and permits one to experiment under better defined conditions and in a way which is similar to true infection.

The investigation of the activity of bacteriophage against the typhoid bacillus was given impetus by the finding of Sertic and Boulgakov[75] and of Craigie and Brandon[35] that the susceptibility of the organism to the action of bacteriophage is closely associated with the presence of Vi antigen. This has been confirmed in other countries (Scholtens;[27] Almon, Read and Stovall[76]). Scholtens demonstrated that secondary colonies from bacteriophage plaques are O forms.[27] Paratyphoid C strains adsorb Vi bacteriophages; however, they are not dissolved by them (Scholtens[77]). Craigie and Yen[78] recently found that a number of types of bacteriophage against Vi forms exist. These are distinguished by their different antigenic qualities and by their action on different strains of the organisms. It is therefore likely that the typhoid bacillus exists in different types whose fine differences are at present recognizable only by means of their different susceptibility to the different bacteriophages. Craigie and Yen[78] were able to demonstrate the relative uniformity of strains derived from a common epidemiologic source by means of their susceptibility or resistance to different types of bacteriophage.

70. Fisk, R. T.: Proc. Soc. Exper. Biol. & Med. **38**:659, 1938.
71. Buttle, G. A. H.; Parish, H. J.; McLeod, M., and Stephenson, D.: Lancet **1**:681, 1937.
72. Siler, J. F.: Mil. Surgeon **80**:91, 1937.
73. Meyer, K.; Smyth, E. M., and Palmer, J. W.: J. Biol. Chem. **119**:73, 1937.
74. Anderson, C. G., and Oag, R. K.: Brit. J. Exper. Path. **20**:25, 1939.
75. Sertic, V., and Boulgakov, N. A.: Compt. rend. Soc. de biol. **122**:35, 1936.
76. Almon, L.; Read, J., and Stovall, W. D.: Am. J. Pub. Health **27**:357, 1937.
77. Scholtens, R. T.: J. Hyg. **37**:315, 1937.
78. Craigie, J., and Yen, C. H.: Canad. Pub. Health J. **29**:448 and 484, 1938. Craigie, J.: ibid. **30**:37, 1939.

Scholtens [79] demonstrated physical differences of various antigenic types of typhoid bacilli by the method of acid agglutination; Vi forms have maximal agglutinability at a p_H of about 2.2, whereas the H antigen is agglutinated at about p_H 4.6. These findings are in accordance with observations of Malek.[80]

At this place it may be mentioned that some observations of Malek's [80c] as well as of Giovanardi's [81] point to a connection between Vi and H antigen, which seems to merit further attention. Possibly, Henderson's findings on complement fixation of live Vi-H bacillus could be interpreted in a similar sense.[82]

Rough and smooth forms were shown by Hirsch [83] and Giovanardi [81] to be different in their flocculability by acriflavine hydrochloride; this is in correlation with the long known difference in stability in salt solutions.

The evidence accumulated since Felix' [21] first description shows that practically all strains freshly isolated from cases of human infection contain Vi. The data compiled by different authors (Felix, Krikorian, and Reitler; [84] Kauffmann; [38] Bhatnagar and others; [85] Malek; [37] Onetto and others; [86] Craigie and Brandon; [35] Almon, Read and Stovall; [76] Horgan; [87] Welch and Mickle [88]) differ only in the relative frequency of Vi forms and intermediate forms (V-W forms of Kauffmann).

It seems increasingly advisable to add Vi antiserum to the usual array of H and O antiserums for routine identification of typhoid bacilli isolated from feces, blood and other material. The preparation of such serum was first feasible only by absorbing serum containing H, O and Vi antibody with an OH strain—for instance, H-901. Felix and Pitt [25] then found more or less rough strains of the type ViH, and recently Bhatnagar [89] described a strain of this type, which he obtained from Kauffmann; he found it to be so poor in flagellar antigen that antiserum prepared with it is practically pure Vi antiserum. The availability of such strains promises to facilitate greatly the preparation of Vi antiserum.

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79. Scholtens, R. T.: J. Hyg. **38**:273, 1938.

80. (*a*) Malek, I.: Compt. rend. Soc. de biol. **129**:788, (*b*) 795 and (*c*) 797, 1938.

81. Giovanardi, A.: Ztschr. f. Hyg. u. Infektionskr. **120**:273, 1937.

82. Henderson,[82] table 3.

83. Hirsch, W.: J. Path. & Bact. **44**:349, 1937.

84. Felix, A.; Krikorian, K. S., and Reitler, R.: J. Hyg. **35**:421, 1935.

85. Bhatnagar, S. S.; Speechly, C. G. J., and Singh, M.: J. Hyg. **38**:663, 1938.

86. Onetto, E.; Leyton, G., and Luna, N.: Rev. d. Inst. bact. de Chile **6**:55, 1937.

87. Horgan, E. S.: J. Hyg. **36**:368, 1936.

88. Welch, H., and Mickle, F. L.: Am. J. Pub. Health **27**:351, 1937.

89. Bhatnagar, S. S.: Brit. M. J. **2**:1195, 1938. Bhatnagar and others.[85]

Felix, Krikorian and Reitler [84] found Vi antibody in serum from patients with typhoid fever and in serum from typhoid bacillus carriers. Men behave like animals inasmuch as they also generally show low titers of antibodies for Vi antigen (confirmed by Almon, Read and Stovall [76]). On the other hand, it seems that titers as low as 1 : 10 are significant. Whereas Vi antibodies are observed in the serums of acutely ill persons and convalescents only irregularly, they are found rather constantly present in the serum of carriers (Felix; [90] Bhatnagar; [89] Lewin [91]). This is of considerable practical interest, as it furnishes an additional diagnostic aid in the detection of carriers.

In this connection, it should be mentioned that carriers harbor, as a rule, smooth strains more or less rich in Vi and not R strains, as one would be inclined to suppose. The transition from S into R forms in typhoid bacilli seems to be ruled by influences quite other than those which rule such a transition in, for instance, the pneumococci. One may even ask whether R variants of typhoid bacillus are really "physiologic" forms or whether they merely appear under the artificial conditions of culture.

Active immunization against typhoid fever underwent an extensive test in the Italian army during the Abyssinian campaign (Castellani [92]). The value of this experience is somewhat impaired by the fact that the predominance of diseases against which no method of active immunization is available was similarly diminished by methods of general sanitation. Nevertheless, it is a feat that typhoid fever was practically not existent in the Italian army.

The question of the best method of active immunization has been investigated from a variety of aspects. Since Grinnell's [93] study established the importance of "smoothness" for the immunizing effect, general consent exists over the necessity of using only strictly smooth strains for the preparation of vaccine (see, for instance, the articles by Brown [94] and Dennis and Berberian [95]). Dennis and Senekjian [96] suggested the measurement of opsonic activity of human blood as a method of gaging immunity. Mollari, Reedy and Randall [8] found considerable protective qualities against infection of the mouse with Salmonella enteritidis, which contains the somatic factor "IX" as does the typhoid bacillus in human serum after typhoid vaccination.

90. Felix, A.: Lancet **2**:738, 1938.

91. Lewin, W.: Typhoid Fever on the Witwatersrand: Bacteriological Aspects, Serological Diagnosis, Specific Prophylaxis and Specific Treatment, Publication 41, South African Institute for Medical Research, Johannesburg, 1938, vol. 7, p. 413.

92. Castellani, A.: Mil. Surgeon **81**:1, 1937.

93. Grinnell, F. B.: J. Exper. Med. **56**:907, 1932.

94. Brown, M. H.: Canad. Pub. Health J. **27**:170, 1936.

95. Dennis, E. W., and Berberian, D. A.: Am. J. Hyg. **20**:469, 1934.

96. Dennis, E. W., and Senekjian, H.: Am. J. Hyg. **26**:11, 1937.

A detailed description of the methods used by the United States Army Medical School for the preparation of vaccines was given by Holt and Hitchens.[97] The United States Army Medical School also conducted investigations to determine the most appropriate strain (Siler [98]). They used protection in mice as a criterion in the evaluation of immunizing activity. Of special importance seems to be the observation by Siler and Dunham [99] that for revaccination a single small intradermal injection is as effective as the repeated subcutaneous ones generally used.

Subcutaneous administration of formaldehyde-killed suspensions of typhoid bacilli is still the predominant method. Tuft [100] was the first to recommend intradermal vaccination against typhoid fever. He found that one seventh to one tenth of the usual subcutaneous dose applied intradermally was sufficient to evoke a satisfactory response, and he reported considerably fewer undesirable reactions. Perry [101] reported the same results in a more recent paper.

The oral administration of vaccine (typhoral [Lilly] preceded by bile salts) has met with approval (Crimm and Short; [102] Moor and Brown [103]) and criticism (Dennis and Berberian; [95] Lewin [91]).

Stuart and Krikorian [104] found deterioration of the immunizing effect with aging of vaccines. This observation may explain why occasionally vaccines made from local strains were found to be more effective than those obtained from abroad (Grasset [105]).

Grasset and Lewin [106] used successfully alum precipitated, formaldehydized lysates ("anatoxin").

Bhatnagar and co-workers [107] advised not more than a one year interval between the first and the second vaccination. This opinion may be conditioned by the special necessities of India, where this work was done. The length of time during which antibodies remain in the serum is set forth in Siler's statistics.[99]

As far as one knows at the present time, the usual vaccines do not evoke Vi antibody in man (Bhatnagar and others; [107] Siler and Dunham [99]). Hence man in his ability to form Vi antibody seems to follow the pattern of horses rather than that of rabbits, which are able to

97. Holt, R. L., and Hitchens, A. P.: Pub. Health Rep. **52**:829, 1937.
98. Siler, J. F.: Am. J. Pub. Health **26**:219, 1936.
99. Siler, J. F., and Dunham, G. C.: Am. J. Pub. Health **29**:95, 1939.
100. Tuft, L.: J. Infect. Dis. **50**:98, 1932.
101. Perry, R. M.: Am. J. Hyg. **26**:388, 1937.
102. Crimm, P. D., and Short, D. M.: Am. J. M. Sc. **196**:826, 1938.
103. Moor, H. D., and Brown, J. L.: J. Lab. & Clin. Med. **22**:1216, 1938.
104. Stuart, G., and Krikorian, K. S.: Lancet **2**:645, 1934.
105. Grasset, E: J. M. A. South Africa **4**:380, 1930.
106. Grasset, E., and Lewin, W.: Compt. rend. Soc. de biol. **125**:979, 1937.
107. Bhatnagar, S. S.; Freeman, J. F., and Dhilon, J. C. S.: Indian J. M. Research **24**:597, 1937.

respond to formaldehydized Vi antigen. However, in making such a statement one must not forget that human beings receive only small doses of vaccine in comparison with the doses used in the hyperimmunization of animals. Thus, lacking the means of evoking Vi antibody in man, one must regard the question whether Vi antibody would improve the protection by vaccination as an academic one. Whether the use of purified antigens in the immunization of man would render it possible to obtain Vi antibodies by vaccination is a still unsolved problem. As pointed out earlier in this article, "complete antigens" are fully antigenic in animals; however, the stimulative effect is not quite as satisfactory as that of vaccines (Felix and Petrie;[108] our own unpublished experiences).

According to Maccolini,[109] addition of alum, hydrous wool fat and other substances used to enhance the immunizing properties of true toxin has no effect if the substance is added to "complete antigens."

For the treatment of typhoid fever, vaccines were used only in a few places during recent years. Frowley[110] reported on his experiences with lysates of typhoid bacilli for therapeutic use, following recommendations originating from Caronia. These lysates are prepared by adding human blood to the cultures and allowing it to exercise its bacteriolytic power. Lewin[91] used "endotoxoid" vaccines, according to Grasset[46] (formaldehydized typhoid bacilli lysates).

Lewin[91] reported favorably on the use of serum prepared by immunization of horses with the formaldehydized autolysates of Grasset,[46] thus confirming Grasset's observation (Gory and Grasset;[111] Grasset and Lewin[112]).

Even more encouraging are reports on the therapeutic effect of a preparation produced by Felix[113] at the Lister Institute. Felix and Petrie[108] recently described in detail methods for the preparation of such serum, and Felix,[114] his methods of assay.[114b] The horses are treated with vaccines made from O strains killed with alcohol (Felix found that such preparations preserve the antigenicity better than the usual formaldehydized vaccines) and subsequently with live rough Vi strains for the stimulation of an additional output of Vi antibody.

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108. Felix, A., and Petrie, G. F.: J. Hyg. **38**:673, 1938.
109. Maccolini, R.: Boll. Soc. ital. di biol. sper. **13**:900 and 1079, 1938.
110. Frowley, J. M.: California & West. Med. **48**:415, 1938.
111. Gory, M., and Grasset, E.: Compt. rend. Soc. de biol. **98**:435, 1928.
112. Grasset, E., and Lewin, W.: Brit. J. Exper. Path. **18**:460, 1937.
113. Felix, A.: Lancet **1**:799, 1935.
114. Felix, A.: J. Hyg. **38**:750, 1938.

114b. Recommended provisionally as standard by the Health Organization of the League of Nations (Report on the Meeting of Serologists of the Permanent Commission on Biological Standardisation, Bull. Health Organ., League of Nations **7**:701, 1938).

The treatment with live bacilli seems to be well tolerated by the horses. There is only one report (Petrie [115]) of bacilluria in a horse after such treatment, but even this horse did not have positive blood cultures. The serum is concentrated by salting out with ammonium sulfate. Reports are uniformly favorable as to the effect of the serum on mortality, fever, toxic symptoms and duration of the disease (Felix;[113] McSweeney;[116] Robertson and Yu;[117] Lewin;[91] Cookson and Facey [118]).

It is generally agreed that the earlier during the course of the infection serum treatment is started the greater is the expectancy of a satisfactory result.

The prophylactic use of such serum was attempted recently during a local epidemic in England (Fenton and Hay [119]). The authors have abstained from any definite statement as to its usefulness, because of the small number of persons treated. Their experience seems to justify their recommendation of further trials in that direction. Topley [120] discussed the advisability of combining prophylactic application of serum with active immunization by vaccine in cases in which there is immediate danger of infection; in such cases the passive immunization could possibly bridge the interval between the beginning of active immunization and the point at which actual active immunity is achieved.

Shwartzman, Baehr and Hollingsworth [121] reported on a series of 80 cases of typhoid fever in which treatment was carried on with a serum obtained from horses immunized with typhoid filtrates. The inhibitive effect on the Shwartzman phenomenon was used as the experimental measure of the activity of the serum (Shwartzman [122]).

A study of Rosenheim [123] on the action of enzymes may be mentioned here as a possible first step in the direction of future purification of typhoid antiserum parallel to recent methods of treatment of antitoxins (Weil, Parfentjev and Bowman [124]). Rosenheim found O antibodies easily destroyable by pepsin, trypsin and papain. H antibodies

115. Petrie, G. F.: J. Path. & Bact. **42**:75, 1936.

116. McSweeney, C. J.: Brit. M. J. **2**:1118, 1937.

117. Robertson, R. C., and Yu, H.: Brit. M. J. **2**:1138, 1936.

118. Cookson, H., and Facey, R. V.: Brit. M. J. **1**:1009, 1937.

119. Fenton, Y., and Hay, C. P.: Brit. M. J. **1**:1090, 1938.

120. Topley, W. W. C.: Lancet **1**:181, 1938.

121. Shwartzman, G.; Baehr, G., and Hollingsworth, W. Y.: Arch. Int. Med. **58**:799, 1936.

122. Shwartzman, G.: Phenomenon of Local Tissue Reactivity and Its Immunological, Pathological and Clinical Significance, New York, Paul B. Hoeber, Inc., 1937.

123. Rosenheim, A. H.: Biochem. J. **31**:54, 1937.

124. Weil, A. J.; Parfentjev, I. A., and Bowman, K. L.: J. Immunol. **35**: 399, 1938.

obtained from horses immunized for several weeks behave in much the same way. However, serum from horses immunized for a longer period were found to contain an H antibody considerably more resistant to the action of pepsin and trypsin—an interesting example of variability of antibodies.

Asheshov, Wilson and Topley [125] obtained a remarkable therapeutic effect with bacteriophage in experimental typhoid infection of mice when microbes and bacteriophage were injected simultaneously. The effect was considerably lessened if bacteriophage was introduced four hours *post infectionem*. The results were confirmed by Fisk.[70] One will recall the French endeavors of treating typhoid fever with bacteriophage (d'Herelle [126]).

As in almost every other disease, sulfanilamide has been tried in the treatment of typhoid fever. Buttle [127] found some activity of the drug in experimental infection of mice. McIntosh and Whitby [128] found that agglutinins developed in mice infected with sublethal doses of the Vi strain the same as in the controls. There have since been a few clinical trials (Diefenbach and Yuskis; [129] Barum [130]). The small number of patients treated does not allow one to draw conclusions as to the effect of the drug.

Our insight into the causes which make the typhoid bacillus (in contrast to so many other related micro-organisms) the etiologic agent of a disease strictly confined to man and characteristic in its pathologic effect is poor. A wide field for the experimental pathologist is still open here. We have clues in different directions which could help in starting an analysis by methods of experimentation. Oerskov and Kauffmann [131] studied the manner of infection with different members of the Salmonella group in mice. Within the Salmonella group one finds all types of infectivity for mice; infection with the typhoid bacillus requires a very large number of organisms even when these are introduced parenterally, unless helped by the addition of mucin; S. paratyphi B is lethal when introduced parenterally in moderate numbers (thousands); Salmonella breslau introduced orally gives rise to a general infection. Oerskov demonstrated that all these bacteria are able to penetrate the enteric wall and yet they do not progress farther than the regional lymph glands, with the exception of the Breslau bacilli, which migrate through

125. Asheshov, J. N.; Wilson, J., and Topley, W. W. C.: Lancet **1**:319, 1937.

126. d'Herelle, F.: The Bacteriophage and Its Behavior, translated by G. H. Smith, Baltimore, Williams & Wilkins Company, 1926.

127. Buttle, G. A. H.: Lancet **2**:1076, 1937. Buttle and others.[71]

128. McIntosh, J., and Whitby, L. E. H.: Lancet **1**:431, 1939.

129. Diefenbach, W. E., and Yuskis, A. S.: California & West. Med. **49**:146, 1938.

130. Barum, R.: Lancet **2**:964, 1937.

131. Oerskov, J., and Kauffmann, F.: J. Hyg. **36**:5141, 1936.

the lymph glands into the general circulation and are thence carried into the organs, where they multiply and reenter the blood stream when multiplication has progressed further; finally the organisms reappear in the feces (if death has not intervened). There is good reason to believe that human typhoid fever is essentially similar to the Breslau infection in the mouse.

But with this analogy knowledge comes to an end. All the data mentioned in this review do not give a satisfactory explanation of the underlying differences between the typhoid bacillus and its harmless and often commensal relatives.

A method of analysis which may help to solve this problem is indicated by the recent work of Goodpasture and Anderson.[132] These investigators started by observing the processes which take place when the chorioallantoid membrane of the chick embryo is infected with the typhoid bacillus; they demonstrated that the reaction differs greatly from that to other micro-organisms. They found that the growth of the typhoid bacillus occurs preponderantly within the body of certain cells, which they identified as plasma cells. (It would be interesting to know with what variant of the typhoid bacillus these experiments were done.) In a subsequent study, Goodpasture[133] found a quite similar situation in human material. He demonstrated that here also the typhoid bacillus is taken up into the bodies of the plasma cells and that it multiplies there. The destruction of typhoid bacilli takes place only if the plasma cells filled with bacilli or the free micro-organisms are phagocytosed by macrophages. These observations show how careful one should be with the equation: phagocytosis = defense reaction. Goodpasture has not yet included other gram-negative rods of the colon bacillus–dysentery bacillus–Salmonella group in his experiments; therefore the question is still open as to whether the typhoid bacillus occupies an exceptional position within this group.

132. Goodpasture, E. W., and Anderson, K.: Am. J. Path. **13**:149, 1937.
133. Goodpasture, E. W.: Am. J. Path. **13**:175, 1937.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, Etc.—The American Society for Experimental Pathology has elected E. W. Goodpasture, president; Shields Warren, vice president; Paul R. Cannon, secretary-treasurer. The next meeting will be held in New Orleans in March 1940, in conjunction with the Federation of American Societies for Experimental Biology.

On account of Robert Moore assuming the professorship of pathology in Washington University School of Medicine, St. Louis, Charles T. Olcott has been elected secretary of the New York Pathological Society.

Institute on Blood Diseases.—The University of Wisconsin Medical School is to conduct an institute for the consideration of blood and blood-forming organs, Sept. 4 to 6, 1939. The program will include reading of papers and round table discussions by European and American workers in the field of hematology. Formal papers will be presented by the following:

L. J. Witts, Oxford, England: "Anemias Due to Iron Deficiency"
Cecil J. Watson, Minneapolis: "The Porphyrins and Diseases of the Blood"
Cornelius P. Rhoads, New York: "Aplastic Anemia"
E. Meulengracht, Copenhagen: "Some Etiological Factors in Pernicious Anemia and Related Macrocytic Anemias"
Harry Eagle, Baltimore: "The Coagulation of Blood"
George R. Minot, Boston: "Anemias of Nutritional Deficiency"
Russell L. Haden, Cleveland: "The Nature of the Hemolytic Anemias"
Jacob Furth, New York: "Experimental Leukemia"
Claude E. Forkner, New York: "Monocytic Leukemia and Aleukocythemic Leukemia"
Edward B. Krumbhaar, Philadelphia: "Hodgkin's Disease"
Louis K. Diamond, Boston: "The Erythroblastic Anemias"
Edwin E. Osgood, Portland, Ore.: "Marrow Cultures"
Charles A. Doan, Columbus, Ohio: "The Reticulo-Endothelial System"
Hal Downey, Minneapolis: "Infectious Mononucleosis"
Paul Reznikoff, New York: "Polycythemia"

Physicians and others who are interested are cordially invited. A detailed program may be obtained by addressing Ovid O. Meyer, chairman of the Program Committee, University of Wisconsin Medical School, Madison, Wis.

Society News.—The annual meeting of the Biological Photographic Association will be held September 14-16, at the Mellon Institute for Industrial Research, Pittsburgh. The program will be of interest to scientific photographers, scientists who use photography as an aid in their work, teachers in the biologic fields, technical experts and serious amateurs. It will include discussions of motion picture and still photography, photomicrography, color and monochrome films, processing and other procedures in the field of scientific illustrating. Up-to-date equipment will be shown in the technical exhibit; and the print salon will display the work of many of the leading biologic photographers here and abroad. The *Biological Photographic Association Journal* is published quarterly, constituting a volume of about 250 pages, which is furnished free to members. Membership privileges include the use of an authoritative question and answer service and the right to borrow loan albums and exhibits of scientific prints for study and display. For further information, write to the Secretary of the Biological Photographic Association, University Office, Magee Hospital, Pittsburgh.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Regeneration of the Adrenal Gland Following Enucleation. D. J. Ingle and G. M. Higgins, Am. J. M. Sc. **196**:232, 1938.

When one adrenal gland is enucleated and the other removed, adequate cortical regeneration proceeds within the enucleated gland. When one adrenal gland is enucleated and the other left intact, there is no, or only very slight, regeneration within the enucleated gland. The presence of the functioning gland suppresses regeneration within the enucleated gland. If a normal adrenal gland is removed eight weeks after enucleation of the other gland, regeneration within the enucleated gland is then stimulated to occur in the normal way. Daily oral administration of 5 cc. of an extract of adrenal cortex completely suppresses regeneration within an enucleated gland even when the other adrenal gland has been removed. Subcutaneous administration of amounts of the extract comparable to those given by mouth will restrict but not completely suppress cortical regeneration within the enucleated gland. Hypophysectomy coupled with enucleation of both adrenal glands completely suppresses regeneration of the cortical tissue. In the presence of half of the anterior lobe of the pituitary there is normal regeneration in the enucleated adrenal glands.

From Authors' Summary.

Effect of Sex Hormones on the Renal Excretion of Electrolytes. G. W. Thorn and L. L. Engel, J. Exper. Med. **68**:299, 1938.

In normal male dogs subcutaneous injections of progesterone, estrone (i. e., theelin), alpha-estradiol or testosterone propionate were followed by decreases in the sodium and chloride excreted in the urine. Marked differences were noted in the potency of these compounds and in the duration of the effects following single subcutaneous injections. The injection of estrone, alpha-estradiol or testosterone propionate was followed by a decrease in the inorganic phosphorus and total nitrogen excreted in the urine. On the day of injection of progesterone, estrone, alpha-estradiol or testosterone propionate a slight increase in the potassium excreted in the urine frequently followed. Experiments on adrenalectomized dogs indicated that the effect of the gonadotropic substances on the renal excretion of electrolytes was not necessarily mediated through the adrenal gland. With the possible exception of progesterone, none of the compounds studied was effective in prolonging the life of adrenalectomized male dogs.

From Authors' Summary.

Experimental Cholecystitis. H. G. Aronsohn and E. Andrews, Surg., Gynec. & Obst. **66**:748, 1938.

By retrograde introduction of a fine ureteral catheter through an opening in the common duct and subsequent plastic repair of the latter a nontraumatic technic was devised for introducing substances into the dog's gallbladder. Most strains of bacteria, even when injected in overwhelming numbers, did not cause cholecystitis unless trauma was an added factor. Carbon dioxide and chlorine were absorbed rapidly from the normal gallbladder, while phosphorus was excreted, but an unknown anion accounted for much of the acidification. Egg albumin injected into a dog's gallbladder set up acute inflammation. An injec-

tion of bile salts produced changes which on gross and microscopic examination closely resembled those found in human cholecystitis. The differences in the activity of different fractions of bile were mainly quantitative; desoxycholic acid proved to be the most effective fraction, causing gangrene of the gallbladder and death of the animal in many instances, while purified and hydrolyzed bile salts were somewhat weaker. Glycocholic acid caused a marked reaction only in the higher concentrations. Deproteinized dog or ox bile left the wall of the dog's gallbladder unchanged. No protective action of protein, as described in the literature, could be demonstrated. Replacement of normal dog bile by bile concentrated to about half its volume had a marked effect. Changes in the hydrogen ion concentration of bile rarely brought about a reaction in the wall of the gallbladder unless they were extreme, less than 3 and greater than 10. Such ranges are not likely to arise in man. The toxic effect of bile salts is not due to a change in their hydrogen ion concentration. It is possible to produce experimentally an allergic condition in the gallbladder. Intravenously injected egg albumin caused edema of the gallbladder wall in previously sensitized dogs, while it caused no reaction in control animals. A pronounced edema was produced by intravenously injected bile salts. This was observed to occur within three minutes after the injection. It is suggested that a temporary increase in the concentration of bile salts in the human gallbladder brings about cholecystitis.

FROM AUTHORS' SUMMARY (WARREN C. HUNTER).

BONE CHANGES IN EXPERIMENTAL HYPERTHYROIDISM AND IN EXOPHTHALMIC GOITER. J. MARTOS, Beitr. z. path. Anat. u. z. allg. Path. **100**:293, 1938.

Experimental hyperthyroidism in rabbits and guinea pigs, induced by multiple subcutaneous injections of thyroxin, brought about osteoclastic lacunar atrophy, most pronounced in the tibia and mandibles. Systematic investigation of the skeletal systems of 12 persons with exophthalmic goiter revealed nonspecific osteoclastic lacunar atrophy in eleven, most intense in the femur and accompanied by proliferation of a fiber-rich connective tissue in the secondarily dilated haversian canals. In places these changes completely mimicked generalized fibrous osteitis. The differences between the bony lesions in man and experimental animals were essentially quantitative; the lesions in the former were more intense because of their longer duration. No anatomic changes were present in the parathyroid glands.

The author agrees with Askanazy that thyroxin is the immediate etiologic factor, and the atrophy of bone is the result of hyperfunction of the thyroid gland.

R. J. LEBOWICH.

Pathologic Anatomy

VARIETIES OF SINGLE CORONARY ARTERY IN MAN, OCCURRING AS ISOLATED CARDIAC ANOMALIES. E. B. KRUMBHAAR and W. E. EHRICH, Am. J. M. Sc. **196**:407, 1938.

Two cases of absence of a coronary artery are reported, in both of which the observation was incidental at autopsy, the anomaly apparently having caused no damage to the myocardium. In the first case a large left coronary artery continued around the auricular-ventricular groove to the anterior surface of the right ventricle, giving off branches that corresponded to those normally given off by both arteries (Hyrtl's type of absence of the coronary artery). In the second case a large right coronary artery supplied most of the heart with conventional branches. Near its origin, however, it gave off one large anomalous branch, which passed behind the aorta to supply a good part of the left ventricle, and another, to the ventricular septum. The possibility must be considered that the former of these represented a true left coronary artery arising from a misplaced anlage, though the similar cases of Bochdalek and Sanes make this very unlikely. Other cases of absence of a coronary artery or possibly of misplacement of the anlage are tabulated, all but 3 of which fall into two groups corresponding to the types described here.

FROM AUTHORS' SUMMARY.

BLOOD VESSELS IN LUNGS. R. D. WRIGHT, J. Path. & Bact. **47**:489, 1938.

In lungs from human cadavers the pulmonary and bronchial arteries and their branches have been injected to show their distribution in pathologic lesions. Proliferative tuberculous lesions and actively growing chorionic carcinomas are avascular. The fibrous scars of tuberculous and silicotic lesions have vessels injected from the bronchial artery. The vessels which develop in fibrosarcomas growing in the lung are injected from the bronchial arteries. If in the adult lung there develops a tissue which is usually supplied from the systemic arterial circulation, the vessels which grow with it are injected from the bronchial artery. This development of new vessels from the systemic arteries may be closely linked with the excitation of collagenous tissue to further development, irrespective of the nature of the agent causing the collagenous proliferation.

FROM AUTHOR'S SUMMARY.

GENETICS OF TRANSPOSITION OF VISCERA. E. A. COCKAYNE, Quart. J. Med. **7**: 479, 1938.

The thoracic and abdominal organs are at first median and symmetric. Transposition of the viscera consists in formation of a sinistral instead of a dextral spiral. Complete transposition of the viscera is inherited as a recessive and is determined by a single autosomal gene. Proofs of this are found in its familial incidence and general distribution within a family, its occurrence in both twins of a monozygotic pair and the high percentage of marriages between first cousins that give rise to it (6 in 52 consecutive fraternities). The ratio of affected to normal sibs in the fraternities, so far as this can be ascertained, agrees with that expected of a recessive character. An exceptional case of monozygotic twins, one normal and the other with transposed viscera, has been recorded. Either somatic mutation or the loss of an autosomal chromosome would account for this. Most authors state that there is a great excess of males with the condition, but in my series the excess of males is small. The incidence of congenital morbus cordis is abnormally high in complete transposition of the viscera, and, according to Kartagener, bronchiectasis is commoner than in normal persons. There are three forms of partial transposition of the viscera: that affecting both thoracic and abdominal organs, that affecting only the thoracic organs and that affecting only the abdominal organs. Their relationship to one another and to complete transposition is discussed. Ways by which the genetic identity of the three different forms of partial transposition with one anther and with complete transposition can be proved or disproved are given. For the following reasons it is suggested that all are determined by the same gene rather than by a series of allelomorphic genes: The three forms of partial transposition are not sharply separated; i. e., there is almost perfect gradation leading up to complete transposition. Congenital morbus cordis is much commoner in partial than in complete transposition, and the anomalies of development of the thoracic and abdominal organs that occur occasionally in the complete form are much commoner in the incomplete forms. Developmental anomalies are more likely to occur with sinistral than with dextral rotation of the viscera, even when sinistral rotation is complete; they are much commoner, however when sinistral rotation is incomplete. Since many of the anomalies shorten life the gene is partially lethal.

FROM AUTHOR'S SUMMARY.

ELECTIVE INSULAR (PARA-) AMYLOIDOSIS OF THE PANCREAS. N. GELLERSTEDT, Beitr. z. path. Anat. u. z. allg. Path. **101**:1, 1938.

In 181 autopsies, including only 3 on patients with diabetes, insular amyloid was revealed in the pancreases of about 45 per cent of the persons over 50 years of age. In younger persons such deposition of amyloid was extremely rare and never severe. The deposits of amyloid are interpreted as a peculiar morphologic expression of senility. So-called hyaline degeneration of the islets of Langerhans in diabetes mellitus is identical with insular amyloidosis and is not specific.

R. J. LEBOWICH.

GENESIS OF CONGENITAL HYDROPS. G. LIEBEGOTT, Beitr. z. path. Anat. u. z. allg. Path. **101**:319, 1938.

In 2 instances of congenital hydrops there was observed, in addition to the usual anatomic changes, pronounced enlargement of the strikingly numerous islets of Langerhans in the pancreas and marked increase in the width of the zona reticularis of the adrenal gland, the cells of which in the sudan preparations were loaded with neutral fat. These changes were accompanied by massive storage of glycogen in the myocardium, which was interpreted as an expression of hyperinsulinism. It is conjectured that the hyperplasia of the islets is related to a disturbance of the maternal carbohydrate metabolism, and this conjecture is to be subjected to experimental investigation.

R. J. LEBOWICH.

HYPERTELORISM (GREIG). K. BOJLEN and T. BREMS, Acta path. et microbiol. Scandinav. **15**:217, 1938.

Since 1924, when Greig described the condition of ocular hypertelorism, 42 cases purporting to be cases of this anomaly have been reported. On critical analysis of the reports it is found that only 27 of the 42 cases may be taken with a fair degree of certainty to be cases of hypertelorism in the sense defined by Greig. Some of the errors in diagnosis are attributable to the difficulty of differentiating between this anomaly and other malformations that may be associated with great breadth between the eyes (congenital facial or nasal clefts, tumor formation over the root of the nose, Apert's and Crouzon's cranial dysostoses).

On the basis of these 27 rather well established cases of hypertelorism and the cases recorded in the present article, a review is given of the symptom complex of this deformity (the question of defective intelligence, the physiognomic characteristics and the combination with other deformities and diseases). As to the mental defect in particular, this is by no means a constant feature of the symptom complex, even though the combination of hypertelorism and mental defect probably occurs too often to be considered an accidental coincidence.

Familial hypertelorism is not recognized generally to occur. In this paper mention is made of 11 cases among 24 members of the same family, hypertelorism appearing through five generations as a hereditary deformity, transmitted as a dominant character. So in these cases the question of heredity is elucidated fully.

As to the causes and pathogenesis, the cases reported here furnish no evidence in support of new views. It is a question whether hypertelorism represents a primary disturbance in the development of the bones that may be accompanied by disturbances in the development of the brain, or whether it represents a primary disturbance in the development of the brain that needs not result in mental defect. The hereditary appearance of the deformity in our cases suggests that the primary factor might be looked for in an anomalous development of the prosencephalon.

FROM AUTHORS' SUMMARY.

Pathologic Chemistry and Physics

ROENTGEN RAY DIFFRACTION ANALYSIS AS APPLIED IN PNEUMONOCONIOSIS. H. C. SWEANY and R. KLAAS, J. A. M. A. **112**:610, 1939.

Roentgen ray diffraction analysis is characterized first of all by its great specificity. Nearly all crystalline compounds give patterns each distinctly different from the others. Hence, when chemical methods are not available for identification of the type of silica present and when microscopic methods are inadequate for the study of mineral particles of the size encountered in tissue, the roentgen method gives definite information as to the identity of the crystalline substances present. Furthermore, a comparison of the patterns with regard to

the nature of the lines, i. e., whether they are smooth or dotted, indicates that there is a variation in size of particles from case to case. In general, it may be concluded that the particles are 1 micron or less in diameter. Further work remains to be done on this aspect of the problem.

Another advantage of the roentgen technic described is that the tissue can be used for analysis unmodified by chemical treatment. Whenever the tissue is digested with some reagent one must make the questionable assumption that no changes take place in the mineral deposits. In the authors' work such an assumption has been unnecessary.

A further significant feature is the great sensitivity of the method. With the present technic the authors are able to detect quartz in a concentration as low as 0.2 per cent. This concentration has been found in previous work to constitute the threshold of the pathologic level. Hence, the finding of a faint line on the roentgen film corresponding to the 3.34 angstrom unit spacing of quartz appears to be a good indication of the presence of sufficient quartz to have already caused, or to be in the process of causing, specific fibrosis in the tissue. Thus the method should be of value in medicolegal work whenever difficulty is experienced in determining the presence or absence of silicosis. FROM AUTHORS' SUMMARY.

BEHAVIOR OF THE HEMOGLOBIN AFTER BLOOD TRANSFUSION. W. L. SIBLEY and J. S. LUNDY, Surg., Gynec. & Obst. **67**:293, 1938.

In the average case in which 500 cc. of citrated blood was given by transfusion there was an increase in hemoglobin of about 1.5 Gm. in 100 cc. of blood (about 9 per cent). This took place at the end of the second day after transfusion. The addition to the hemoglobin tended to decrease to about 1 Gm. in 100 cc. by the tenth day after transfusion. An increase in the hemoglobin of 2.12 to 2.8 Gm. in 100 cc. (12.72 to 16.8 per cent) could be anticipated in cases in which the patient showed no reaction or bleeding following transfusion. The amount of increase in the hemoglobin of the recipient of 500 cc. of citrated blood was directly proportional to the value for hemoglobin before the transfusion. As a rule, there was definitely less increase (usually 50 per cent) in the hemoglobin of the recipient when a reaction to transfusion occurred than when none occurred.

FROM THE AUTHORS' SUMMARY (WARREN C. HUNTER).

DISAGGREGATION OF PROTEINS BY ENZYMES. C. G. POPE, Brit. J. Exper. Path. **19**:245, 1938.

A preliminary report is made on the action of fibrinolysin in producing disaggregation of the molecule of antitoxic pseudoglobulin into its protein components, each having different physical and chemical properties. Such action is not limited to fibrinolysin but appears to be a property of all proteolytic enzymes, provided they are used under the correct conditions. By taking advantage of this property of enzymes, Pope evolved a method of critical differential heat denaturation for the further purification of antitoxins. To be of use in this method the action of the enzymes must be so limited that no hydrolysis or digestion in the generally accepted sense takes place; if this occurs, differential denaturation fails, because obviously it cannot affect noncoagulable protein fragments. Based on the methods outlined, a process for large scale purification of antitoxins has been evolved and will form the subject of other papers. As a point of interest it may be stated that by the use of these methods antitoxin has been prepared experimentally which is of such purity that all the protein present can be specifically precipitated by diphtheria toxin. FROM AUTHOR'S SUMMARY.

DIFFUSE ENDOCARDIAL THICKENING IN INFANTS. H. LOH, Beitr. z. path. Anat. u. z. allg. Path. **101**:253, 1938.

In 3 instances of diffuse and uniform fibrosis of the endocardium of the left and right ventricles of the infant heart, errors of development were observed,

such as hypoplasia of the right ventricle. After exclusion of a thrombotic and an inflammatory origin it was concluded that diffuse endocardial fibrosis represents a developmental error.

R. J. LEBOWICH.

Microbiology and Parasitology

PASSAGE OF PNEUMOCOCCI INTO LYMPHATICS. R. Z. SCHULZ, M. F. WARREN and C. K. DRINKER, J. Exper. Med. **68**:251, 1938.

When type III pneumococci that were virulent for rabbits were instilled into the nose or trachea of the animal, they were recovered in the lymph collected from the lymphatics draining the area involved, during a subsequent four hour period. The detection of the organisms rarely failed and not infrequently was possible at the end of the first hour. Practically invariably the organisms appeared in the lymphatics and subsequently in a few cases in the blood during the four hour test period. Intravenous administration of antiserum two and one-half to three hours before the instillation of the organisms decreased the number of animals in which the lymph or the blood was shown to contain the organisms and the total length of time during which the organisms were recoverable in lymph from the efferent lymphatics during the test period.

FROM AUTHORS' SUMMARY.

PROPAGATION OF INFLUENZA VIRUS IN GUINEA PIG FETUS. O. C. WOOLPERT and others, J. Exper. Med. **68**:313, 1938.

The PR8 strain of the virus of human influenza was found to proliferate and disseminate widely in the tissues of fetal guinea pigs, inoculated in utero. After incubation periods ranging from two to six days, large quantities of the virus, free from bacteria, were recovered from lung, liver and placenta and smaller quantities from blood and brain. Although the fetuses proved to be excellent for the propagation of the virus, they evinced grossly little reaction to the infection. Several series of passages from fetus to fetus were accomplished; one consisted of 10 transfers and another of 16. For serial passage the virus was inoculated intracerebrally into half-grown fetuses, and the fetal lungs were harvested forty-eight hours later as a source of virus for subinoculation. It is concluded that multiplication of the virus occurred in the lungs particularly, a conclusion which may be considered a significant reaffirmation of the statement that this virus shows pneumonotropic tendencies. Following passage in series the virus was found, on the basis of cross immunity and cross neutralization tests, to be immunologically identical with the mouse passage virus from which it was derived. Other properties also appeared to be unaltered by passage of the virus under these conditions.

FROM AUTHORS' SUMMARY.

CONDITIONS IN THE SKIN OF TUBERCULOUS GUINEA PIGS AS DEMONSTRATED WITH A VITAL DYE. A. L. JOYNER and F. R. SABIN, J. Exper. Med. **68**:325, 1938.

The skin of tuberculous guinea pigs while it is allergic permits the spread of a vital dye, pontamine sky blue, and the drainage of the dye into the vascular system to take place much more slowly than in the normal animal. The skin of moribund tuberculous guinea pigs, animals no longer allergic, permits dye to spread more rapidly than in the normal animal. In the skin of guinea pigs infected with a hemolytic streptococcus the spread of dye was found to be somewhat restricted. These animals were allergic. The observations suggest that the dye method may disclose altered tissue conditions in the allergic state.

FROM AUTHORS' SUMMARY.

CELLULAR REACTIONS TO TUBERCULO-PROTEINS. F. R. SABIN, J. Exper. Med. **68**:837, 1938.

Tuberculoprotein in solution induces formation of monocytes in animals that are normal and tubercles of epithelioid cells in animals that are tuberculous.

Freshly precipitated tuberculoproteins from the culture mediums and from the bacilli induce moderate formation of epithelioid cells in normal animals and more marked formation of such cells in the tuberculous. Insoluable forms of tuberculoprotein induce complex tuberculous tissue in normal animals. This action is enhanced in the tuberculous animals. FROM AUTHOR'S SUMMARY.

CELLULAR REACTIONS TO DEFATTED TUBERCLE BACILLI. F. R. SABIN and A. L. JOYNER, J. Exper. Med. **68**:853, 1938.

The cellular reactions to defatted tubercle bacilli are complex and like those to heat-killed whole tubercle bacilli. The firmly bound lipid when removed from these organisms is nonacidfast; it contains a hydroxy acid which is acid-fast and a polysaccharide which is not. This hydroxy acid gives rise to foreign body giant cells, and the tissues eventually become infiltrated with eosinophils. The polysaccharides from the defatted bacilli and from the unfiltrable lipid call neutrophils from the blood stream. The reactions to the unfiltrable lipid include those to both its constituents. FROM AUTHORS' SUMMARY.

ON THE INHERITANCE OF THE AGGLUTINOGENS A, B, M AND N. F. E. HOLFORD, J. Infect. Dis. **63**:287, 1938.

The adequacy of the reagents and technics employed in the determination of the agglutinogens A, B, M and N was tested, with satisfactory results, in a random sample comprising 1,100 persons. A more critical test was represented in a study of the inheritance of the same agglutinogens in 100 families with 234 children; it revealed no exceptions to the theory of Bernstein or of Landsteiner and Levine and showed a close approximation of the observed values to the theoretic requirements. A study of 124 mothers with 277 children offered further confirmation of the adequacy of the reagents and procedures employed.

The data, showing no exceptions to the requirements of the theories of Bernstein and of Landsteiner and Levine, offer further confirmation of those theories.

FROM AUTHOR'S SUMMARY.

TOMATO BUSHY STUNT VIRUS. F. C. BAWDEN and N. W. PIRIE, Brit. J. Exper. Path. **19**:264, 1938.

The isolation of a protein, probably the virus itself, from plants infected with tomato Bushy stunt virus is described. Not only does this protein differ from the normal plant proteins, but it differs more from the other purified plant viruses than these differ from one another. It is fully crystalline instead of liquid crystalline. It has a higher nucleic acid content than tobacco mosaic virus or the X virus of potato and is more stable toward p_H changes but less stable toward dehydrating agents. Its particles are not elongated, and liquid and solid preparations are isotropic. One cubic centimeter of a solution containing 10^{-7} Gm. produces infections when rubbed on to Nicotiana glutinosa, and 1 cc. containing 10^{-6} Gm. gives a specific precipitate with antiserum. Precipitates of the rod-shaped viruses obtained with their antiserum resemble those obtained with bacterial flagellar (H) antigens, but those of Bushy stunt virus resemble those obtained with somatic (O) antigens. When irradiated with ultraviolet rays or treated with nitrous acid, the virus loses its infectivity, but it can still be crystallized and it still retains its serologic activity. FROM AUTHORS' SUMMARY.

CYTOPLASMIC INCLUSIONS IN THE ENGORGING TICK. J. D. GREGSON, J. Path. & Bact. **47**:143, 1938.

Cytoplasmic inclusion bodies of the engorging gut cells of Dermacentor andersoni, resembling in many ways certain living symbionts, are described with refer-

ence to their staining reactions and morphologic appearances. They are globoid, and they grow in size from ultramicroscopic dimensions to 15 microns in diameter. They are exceedingly resistant to strong salt solutions, acetic acid and fat solvents. They react feebly with all stains except Mallory's triple stain, in which they are colored crimson; bodies appearing blue by this method are thought to be old and disintegrating. Other inclusion bodies exhibiting similar appearances and staining reactions are described within the engorging tick, and an attempt is made to establish a relationship between them that might lead to understanding of their origin and fate and of their relation to the tick. These other bodies have been noted in the tick's hypodermal cells, ova, spermatozoa and phagocytic cells and in surrounding muscle fibers. To date no success has followed various attempts to culture these bodies, although in several instances forms suggestive of binary fission have been noted.

FROM AUTHOR'S SUMMARY.

TISSUE AFFINITIES OF VACCINE VIRUS. C. LEVADITI, R. FASQUELLE, L. REINIÉ and R. SCHOEN, Ann. Inst. Pasteur **60**:142, 1938.

Vaccine virus is composed of two elements, one (E) having an affinity for ectodermal tissue and the other (M) having an affinity for mesodermal tissue. In bovine dermovaccine the E elements predominate, but in rabbit neurovaccine the M factors are dominant.

Dermovaccine of bovine origin produces little or no reaction when injected intraperitoneally or intrapleurally into rabbits. Neurovaccine gives marked pleural and peritoneal reactions when injected in the ways named.

Dermotropic virus shows a strong affinity for the glandular and excretory organs (kidney and liver) but little affinity for hemopoietic tissue (bone marrow, spleen and lymph nodes) when inoculated directly into these organs. When inoculation is made into organs directly, the functional character of the organs dominates over the factor of embryonic origin, so that organs of mesodermic derivation are invaded by dermovaccine. The mesodermotropic virus attacks both groups of organs. The lymph nodes are least frequently invaded by either virus.

Different strains of dermotropic virus vary greatly in their power to produce encephalitis. Dermovaccine may become quantitatively transformed into neurovaccine by successive intracerebral inoculations into rabbits, so that the epitheliotropic property (E) of Jennerian vaccine becomes secondary to the neurotropic property (M). Nerve tissue and sometimes testicular tissue are selective for dissociation of E to M. This transformation may be produced also by inoculation into embryonic tissue or by passage through certain animal species, especially the rabbit.

This selective transformation is not reversible. If neurovaccine is inoculated intradermally into calves, no macroscopic pustules are produced. The virus can be recovered from microscopic edematous lesions and is unaltered in its neurotropic properties. Serial transfer from calf to calf results in typical pustules after about the third passage. In spite of this enhanced cutaneous virulence for the calf, the recovered virus still produces pleuroperitoneal lesions and encephalitis in the rabbit; i. e., the mesodermatropic affinities are unaltered or may even be augmented.

J. B. GUNNISON.

Immunology

TUBERCULIN PROTEIN AND POLYSACCHARIDE MOLECULES. F. B. SEIBERT and others, J. Exper. Med. **68**:413, 1938.

Studies have been made by means of sedimentation in the ultracentrifuge and by diffusion and electrophoresis to determine the molecular weights and homogeneity of the tuberculoprotein and polysaccharide molecules as found in their natural state in unchanged filtrates from culture mediums after growth of tubercle bacilli. These results have been compared with data obtained on fractions isolated

from them or from old tuberculin by chemical procedures. By means of electrophoresis in the Tiselius apparatus it was possible to separate the protein from the polysaccharide as these two fractions occur naturally in the filtrates from the original culture mediums that have supported growth of acid-fast bacilli.

FROM AUTHORS' SUMMARY.

ANTILYMPHOCYTIC SERUM. W. B. CHEW and J. S. LAWRENCE, J. Immunol. **33:** 271, 1937.

Rabbits were each given twenty-one daily intravenous injections of 0.1 cc. of lymphocytes. These cells had been obtained by grinding lymph nodes of guinea pigs, suspending the pulp in saline solution and filtering. A control serum was prepared by inoculating rabbits with suspensions of ground liver and kidney from mice. Both serums were absorbed repeatedly with the red cells of guinea pigs to remove the hemolytic action and then with the red cells of sheep to remove the Forssman heterophilic fraction. They were then inactivated, preserved with phenol and passed through a Seitz filter. When guinea pigs were given intracardial injections of from 0.25 to 0.35 cc. of the serum, which was very toxic in higher doses, the lymphocytes dropped within a few minutes from an average of over 3,000 to less than 1,000 per cubic millimeter and remained at this level for about six hours, after which their number increased gradually. The number of neutrophils decreased similarly but only for about one hour and then rose rapidly. The control serum was not toxic and caused only a brief rise in lymphocytes. Intra-abdominal injections of the immune serum produced a similar drop in lymphocytes, except that the minimum level lasted longer; there was no drop in the neutrophils, but a marked rise. Repeated intra-abdominal injections brought about a drop in lymphocytes which continued during the entire period of treatment, while the neutrophils showed rises separated by drops. At necropsy the lymphoid tissues were hyperplastic in all animals, including the controls. The bone marrow was hyperplastic but more so in the animal receiving the antilymphocytic serum.

I. DAVIDSOHN.

FLOCCULATION OF ALCOHOLIC RED CELL EXTRACTS BY DIFFERENT TYPES OF HUMAN HETEROGENETIC HEMAGGLUTININS. F. SCHIFF, J. Immunol. **33:** 315, 1937.

Alcoholic extracts of red blood cells of the rabbit, sheep, ox and horse were flocculated only by undiluted normal human serums or by these serums diluted 1:2. Serums of persons who had been treated with horse or rabbit serums gave strong flocculation reactions with the aforementioned extracts; the serums of the latter group flocculated, in addition, extracts of red cells of cats. Serums of patients with infectious mononucleosis flocculated these extracts feebly or not at all. An alcoholic extract of guinea pig kidney (Forssman antigen) was flocculated strongly by a homologous immune serum at 37 C.; it was flocculated weakly at 20 C.; at the same temperature it was flocculated strongly by the serum of a patient with horse serum disease and moderately by the serum of a patient with rabbit serum disease, while the serum of a patient with infectious mononucleosis did not flocculate the extract at either temperature. I. DAVIDSOHN.

IMMUNITY TO THE VIRUS OF PSITTACOSIS. S. P. BEDSON, Brit. J. Exper. Path. **19:**353, 1938.

Immunity to the virus of psittacosis can be produced in mice by means of a formaldehydized vaccine in which no living virus is demonstrable. This immunity lasts for at least three months. The protection obtained is not complete even against small doses of virus, since a test injection of active virus almost invariably results in infection. Multiplication of the virus, however, stops short of that

required for the production of frank disease, the infection remaining silent. This silent infection has been found to last for as long as seven months. Serial passage of virus in immunized mice through five generations and extending over a period of two hundred and ninety days produced no appreciable change in its virulence. Specific antibody can be demonstrated in low concentration in the circulation of immune mice by the neutralization test. The injection into mice of an apparently neutral serum-virus mixture results in a silent infection, which, as in the case of the actively immunized mice, may last for months. The mechanism of immunity to the virus of psittacosis is discussed, and it is suggested that it is principally a function of specific antibody. FROM AUTHOR'S SUMMARY.

STREPTOLYSINS. E. W. TODD, J. Path. & Bact. **47**:423, 1938.

Hemolytic streptococci of group A produce two distinct varieties of streptolysin—streptolysin O, which is sensitive to oxygen, and streptolysin S, which is highly soluble in serum. These are neutralized by separate antibodies, which appear to be entirely unrelated. Reduced filtrates from cultures in dextrose broth contain streptolysin O but not streptolysin S. The streptolysins which are formed by group A strains in sugar-free broth or in serum broth and the hemolytic extracts prepared by Weld's technic are all mixtures of the two lysins. All filtrates of cultures of group A hemolytic strains, including serum-streptolysin, serum-free streptolysin and Weld's hemotoxin, when inoculated into animals cause an increase in the antistreptolysin O titer of the serum but no increase in the antistreptolysin S titer; hence streptolysin O is antigenic, but streptolysin S is apparently not antigenic when separated from hemolytic streptococci. Antibodies to both lysins are formed when animals are inoculated with living cultures of group A hemolytic strains. Patients infected with hemolytic streptococci do not usually acquire high antistreptolysin S titers, although their antistreptolysin O titers may be considerably raised. The relationship between leukocidin and the two forms of streptolysin is unknown. FROM AUTHOR'S SUMMARY.

GENERAL REACTION TO INTRAVENOUS INJECTION OF MELITIN. P. DURAND, Arch. Inst. Pasteur de Tunis **27**:193, 1938.

Intravenous injection of melitin into persons without a history of possible exposure to Brucella melitensis produces no reaction. In persons who are or who have been infected with this organism such an injection produces a marked febrile reaction of several hours' duration. This specific shock is often a more sensitive test for brucella infection than the intradermal reaction. Intravenous and intradermal tests indicated a high incidence of this infection in Tunis, Tunisia. FROM AUTHOR'S SUMMARY.

BLOOD GROUP PROPERTIES IN SHEEP. T. ANDERSEN, Ztschr. f. Rassenphysiol. **10**: 104, 1938.

Of 41 rabbits immunized with human A_1 blood cells, 16 produced group-specific hemolysins for sheep blood. By suitable absorption tests with sheep blood it could be shown that many of these immune serums contained several qualitatively different antibodies, as shown by the reactions of the absorbed serums with various sheep bloods, one serum containing as many as five distinct hemolysins. Andersen explains these reactions by postulating the existence of different partial antigens in different sheep bloods, all of which are present in human A_1 blood. In several cases sheep hemolysins could be absorbed with human O blood, but immunization of rabbits with human O blood failed to elicit sheep lysins. Tests on the blood of 93 sheep with three different absorbed anti-A immune rabbit serums revealed a certain correlation between the reactions of these serums and the three group classification by isohemolysis. Sheep cell lysins obtained by immunizing rabbits with sheep blood were not absorbable by human A_1 blood. A. S. WIENER.

Tumors

CARCINOMA OF THE KIDNEY IN THE LEOPARD FROG. B. LUCKÉ, Am. J. Cancer **34**:15, 1938.

The leopard frog is commonly affected with adenocarcinoma of the kidney. This tumor, as in the case of mammalian neoplasms, remains localized while it is small and in its early stages, but when large it frequently forms secondary tumors in distant organs. The dissemination usually takes place by way of the blood stream. In the present paper Lucké reports 22 new examples of metastasis. His frequent observations of metastasis make the evidence for the malignancy of this tumor complete.

FROM AUTHOR'S SUMMARY.

LEIOMYOMA OF THE ORAL CAVITY. A. P. STOUT, Am. J. Cancer **34**:31, 1938.

Two examples of leiomyoma are reported. One, a vascular type, developed in the base of the tongue and was probably derived from the smooth muscle of blood vessels. The other, a pedunculated tumor springing from the dorsum of the tongue, was probably a dysontogenetic circumvallate papilla. Four other reported examples of leiomyoma in the oral cavity are reviewed. It is suggested that an explanation for the apparently rare occurrence of leiomyoma in the oral cavity is to be found in the paucity of smooth muscle in that part of the body.

FROM AUTHOR'S SUMMARY.

MONOCYTIC LEUKEMIA AND OTHER NEOPLASTIC DISEASES. J. FURTH and O. B. FURTH, Am. J. Cancer **34**:169, 1938.

A leukemia-like disturbance, with malignant cells resembling monocytes, occurred in approximately 9 per cent of 96 mice that received intrasplenic injections of benzpyrene. This disease, hitherto not described in mice, did not occur among an equal number of control mice of the same stock but was observed on rare occasions in different untreated mice of the stocks (Rf) used in these studies. Intrasplenic injection of benzpyrene into mice increased the incidence of pulmonary tumors approximately three times. Microscopically the growth in the mice given benzpyrene was similar to that in the control mice. It appears to originate from the alveolar epithelium, often in several foci in the same animal. Its pathogenesis has not been determined, but in these experiments inhalation of the cancerogenic chemical is excluded. The incidence of myeloid leukemia was greater among the mice receiving the injections than among the controls, but further data are needed to determine a causal relationship between the injections of benzpyrene and the incidence of this disease. In each of 2 animals atypical sarcoma, possibly with its origin in muscle cells, occurred at the site of injection and led to almost complete destruction of the spleen. In the first instance the neoplasm was successfully transmitted to all of 7 mice by means of fragments introduced into the subcutaneous tissue. In 2 mice that received intrasplenic injections of cancerogenic chemicals neoplastic hemangioma of the liver and spleen occurred. Since similar neoplasms are very rare in mice and were not observed among the controls, it is possible that in these mice neoplastic hemangioma was produced by the injected chemical.

FROM AUTHORS' SUMMARY.

INCREASED SUSCEPTIBILITY TO BROWN-PEARCE CARCINOMA. J. W. MU, Am. J. Cancer **34**:407, 1938.

Subcutaneous administration of an estrogenic substance (prepared from a butyl alcohol extract of the urine of pregnant women) to male albino rabbits accelerated the rate of growth of the Brown-Pearce epithelioma at sites of primary implantation and stimulated the development of metastases and also the size of the tumor growths in such foci.

FROM AUTHOR'S SUMMARY.

GROWTH PROCESSES INDUCED BY ESTROGENIC HORMONES. L. LOEB, V. SUNTZEFF and E. L. BURNS, Am. J. Cancer **34**:413, 1938.

Among approximately 500 mice, the majority of which had received injections of various doses of estrogen over different periods of time, microscopic study of the sex organs showed in no case cancerous changes or even true precancerous proliferations. There is reason for assuming that the reactivity of the uterine epithelial structures to growth stimulation is less than that of the corresponding tissues in the vagina, cervix and mammary gland—an assumption which is in accord with the behavior of these tissues during the sexual cycle and during pregnancy. One may therefore conclude that cancerous transformation depends on, among other factors, the product of the intensity of the growth stimuli acting on a tissue and the responsiveness of the affected tissue. There are indications that in a similar manner the transformation of cylindric epithelium into transitional or squamous epithelium also depends on the product of the intensity of certain effect growth stimuli and an inherited responsiveness of these tissues to these stimuli. In a minority of the mice in these experiments certain changes were observed which represent abnormal but noncancerous growth processes, namely, penetration of the uterine glands into or through the musculature of the uterus and metaplasia of the cylindric surface epithelium and perhaps also of some glands into transitional or squamous epithelium. In a considerable number of cases, however, the squamous epithelium owed its origin to regenerative processes which led to extension of the epithelium of the cervix into the uterus. It is possible that in cystic transformation of the uterine glands, also, growth stimulation may be involved. All these changes may occur, although with much less frequency, in control mice not receiving injections of the growth-stimulating factor, becoming as a rule more frequent with advancing age. Under the influence of estrogen they are produced, on the whole, the more readily the greater the dose used and the more continuous its action. FROM AUTHORS' SUMMARY.

CYSTEINE HYDROCHLORIDE IN THE TREATMENT OF ANIMAL TUMORS. J. L. CARR, C. L. CONNOR and L. L. GINZTON, Am. J. Cancer **34**:428, 1938.

The treatment of three different rat tumors and the Brown-Pearce rabbit carcinoma with cysteine hydrochloride was practically ineffective except that direct injection of the drug into the Jensen sarcoma and an adenofibroma of rats caused complete regression and cross immunity between the two. The treatment prolonged the average life of rats bearing the Walker tumor by eleven and one-tenth days. Related substances, even those containing the SH radical (ethyl mercaptan and a compound of aldehydes and thio acids) had no effect. The experiments showed some variation in response in the various tumors treated but showed also that intravenous injections of extremely large quantities of cysteine hydrochloride, which contains the SH radical, produce little effect on a rapidly growing rabbit carcinoma. FROM AUTHORS' SUMMARY.

LYMPHOSARCOMA CELL LEUKEMIA. R. ISAACS, Ann. Int. Med. **11**:657, 1937.

Of 43 patients with lymphosarcoma, 15 entered a leukemic phase. Sternberg called it leukosarcoma, but Isaacs prefers the term "lymphosarcoma cell leukemia." The lymphosarcoma cell has a characteristic feature: a single nucleolus with a deeply hyperchromatic rim. In the immature lymphocyte or lymphoblast there are, as a rule, multiple nuclei without the rim. Supravital staining also shows characteristic features.

Such cells were found already in the aleukemic phase of lymphosarcoma; they constituted from 3 to 30 per cent of cells in the differential count. From the total white cell count of from 6,000 to 10,000 in the aleukemic phase, the cells rose in the leukemic phase to an average of 70,000, and the highest was 156,000 per cubic millimeter. The number of lymphosarcoma cells increased, too, reaching occasionally 98 per cent. There was increasing anemia, with a color index of around

1 or slightly lower. The platelets were normal at first, with a drop later in the disease. The leukemic phase was characterized by exacerbation of symptoms and by fever. The effect of roentgen therapy was not favorable. At the necropsy all the lymphoid tissues were found transformed in varying degrees into the lymphosarcoma type, and an infiltration of almost all organs and tissues was present. The leukemic phase seemed to depend on extensive infiltration of moving organs, particularly the lungs. According to Isaacs, the disease appears to be true lymphosarcoma cell leukemia and not lymphosarcoma turning into lymphatic leukemia.

I. DAVIDSOHN.

RADIOSENSITIVE AND NONRADIOSENSITIVE CARCINOMA OF THE LARYNX. W. HARRIS and P. KLEMPERER, Arch. Otolaryng. **28**:355, 1938.

Harris and Klemperer report on 32 cases of laryngeal carcinoma in which the only treatment was roentgen irradiation (Coutard). In every case the lesion occurred on the epiglottis or within the larynx. The roentgen therapy resulted favorably in 20 of the 32 patients; 12 failed to respond. The biopsy material was studied histologically to determine criteria for pathologic differentiation of radiosensitive and radioresistant carcinoma. The grade of cellular differentiation, the mitotic count, the anaplasia of the cells, the reaction in the stroma and the location of the carcinoma were fully considered. There were no pathologic criteria except possibly the number of mitoses which permit differentiation between radiosensitive and radioresistant laryngeal carcinoma if protracted fractional roentgen therapy is used. The results seem to contradict the belief that radiosensitivity depends on the degree of differentiation of the tumor cells.

IMMUNOLOGIC REACTIONS OF THE VIRUS OF RABBIT PAPILLOMA. J. G. KIDD, J. Exper. Med. **68**:703, 725 and 737, 1938.

The evidence as a whole favors the view that the virus stimulates the formation of the virus-neutralizing and complement-binding antibodies in vivo, and many facts indicate that it is closely associated and in all probability identical with the antigen that reacts with immune serum to fix complement in vitro.

FROM AUTHOR'S SUMMARY.

NORMAL AND PATHOLOGICAL DEVELOPMENTS FROM THE CELLS LINING THE GRAAFIAN FOLLICLE. W. S. GARNER, Surg., Gynec. & Obst. **67**:455, 1938.

Commonly spoken of as germinal epithelium, the layer of cells lining the graafian follicle have been shown by Pedro Ramon to be connective tissue. While this readily explains the normal course of these cells to the formation of the corpus albicans, it makes difficult the explanation of the development from granulosa cells of several types of epithelium in the evolution of pathologic growths. Both of these difficulties are readily obviated if one remembers that the lining cell has the same embryonic origin as the ovum, the latter being merely a cell set apart from its fellows. Since the cells lining the graafian follicle are closely related to the totipotential ovum, it is not surprising that they may, under varying stimuli, produce a variety of types of cells. At first called germinal epithelium, the cells lining the primordial follicle are termed lutein cells after the mature follicle has ruptured; these in turn as they become hyalinized are called connective tissue cells; in the atretic cysts they are known as granulosa cells. Histologically Gardner has traced the development of granulosa cells into several types of epithelium, including the goblet type characteristic of adenocystoma, the papilloma and in a single instance almost certainly the early stages of the formation of a dermoid cyst. The observations were made on small cysts that still retained a part of the original structure so that their nature could not be questioned. Since it is reasonable to assume that the normal changes in the cells of the graafian follicle are due to the action of hormones, it may be speculated whether the abnormal changes are not due to a similar influence.

WARREN C. HUNTER.

MODE OF INCEPTION AND LATERAL SPREAD OF CERTAIN SQUAMOUS CELL CARCINOMAS. A. BRUNSCHWIG and D. TSCHETTER, Surg., Gynec. & Obst. **67**: 715, 1938.

Microscopic study of small, early squamous cell carcinomas of the skin and buccopharyngeal mucosa reveals involvement of a segment of the epithelium rather than origin from one cell or from a small nidus of cells. At the margins are zones of direct continuity between normal and abnormal epithelium where it is impossible to determine which cells are normal and which are neoplastic. Likewise, in some well established carcinomas the presence of long adjacent parallel columns of downward proliferating cells instead of a thin superficial segment affords evidence of a segmental origin of the lesion. It is recognized that besides the aforementioned methods of extension well defined carcinomas may show sharp demarcation or growth under or over the epithelial surface from which they have originated. The hypothesis of progressive cancerization as a factor in the lateral spread of such lesions is not new but has received little emphasis and has never been subjected to experimental tests.

Epidermoid carcinoma was induced in mice by repeated paintings with a 0.3 per cent solution of methylcholanthrene in benzene. By means of india ink tattooings of the skin peripheral to the induced growths it was found that the expanding carcinoma did not push the dots outward but grew over them, thus indicating progressive cancerization rather than expansive spread. Furthermore, a zone of direct continuity between neoplastic and non-neoplastic epithelium was seen where a differentiation between the two was not possible. In another group the carcinoma was bisected, and the healthy skin was approximated to the remaining half of the tumor and allowed to heal. Under these conditions the neoplasm continued to spread on the side opposite the wound but rolled up where the skin had been interrupted. These observations are interpreted to indicate that the normal skin offered resistance to carcinomatous transformation whereas that in direct continuity on the opposite side did not. It is concluded that the experiments offer support for the hypothesis that there is continued lateral spread of certain squamous cell carcinomas by progressive cancerization of normal epithelium at the immediate periphery of the carcinomatous growth, in addition to centrifugal expansion by multiplication of cells. WARREN C. HUNTER.

A METASTATIC DEPOSIT OF BRONCHIAL CARCINOMA IN A HYDROCELE MISDIAGNOSED "ENDOTHELIOMA." R. A. WILLIS, J. Path. & Bact. **47**:35, 1938.

A case is reported in which a large malignant growth in a hydrocele sac was diagnosed as endothelioma of the tunica vaginalis but was shown by postmortem examination to be a metastasis from a small symptomless carcinoma of a bronchus. Some recently reported cases of supposed endothelioma and mesothelioma of serous membranes are critically reviewed. In none of them can this diagnosis be accepted. In regard to the confusing subject of primary celomic tumors, two guiding principles must be adhered to: 1. There are no distinctive histologic criteria of endothelioma. 2. The diagnosis of endothelioma requires that a complete postmortem examination shall have excluded as a possible source of carcinoma each and every epithelial structure in the body. FROM AUTHOR'S SUMMARY.

Technical

BLOOD TRANSFUSION IN AMERICA. P. LEVINE and E. M. KATZIN, J. A. M. A. **110**:1243, 1938.

This survey reveals some increase in the use of the international classification for blood typing. This scientific and logical system will undoubtedly becoume still more popular when a greater number of medical schools teach it rather than the arbitrary, confusing and meaningless numberings.

The general adoption of statutes, similar to those of New York and Wisconsin, authorizing courts to accept the results of blood tests in paternity disputes, will also stimulate the use of the international system, since it is difficult to discuss the genetics of the blood groups in terms of any other classification.

With regard to transfusion methods, it is noteworthy that about one half of the hospitals surveyed employ two methods, the citrate and one or another of the direct methods. Fortunately the great majority of transfusionists employing the direct method use either the multiple syringe procedure or one of the simpler forms of apparatus which are manually operated, and have avoided any apparatus in which the blood flow is regulated by a ball in valve mechanism.

In this country transfusions are for the most part performed, at least in hospital wards, by interns, under the sometimes inadequate supervision of a resident or other member of the attending staff. Of course, the ideal organization for this purpose would appear to be that in which a transfusion team is employed in close association with the laboratory. However, with a rapidly changing house staff, such as is found in the great majority of hospitals, this is apparently believed to be possible only to a limited extent. Yet even under such conditions it is, in the authors' opinion, feasible and practical that this work be done under the direct control of a small number of trained workers, who instruct each new group of interns as they enter the hospital. Furthermore, the persons in charge might then form a liaison between the various hospitals, the local health department and the medical societies to regulate professional donors and to provide a center for the study of problems related to blood transfusion.

Some such cooperative action is required, since, as this survey reveals, many institutions lack adequate control of syphilis in both professional and volunteer donors. Until American hospitals have at their disposal donors from carefully regulated agencies, it seems essential for each hospital to perform a recognized test for syphilis immediately prior to the transfusion. This, however, does not in any way relieve the transfusionist of the responsibility of a careful physical examination of the donor.

Although the practice of selecting a compatible donor by a blood-grouping test of the prospective donor's cells, followed by a direct matching of the donor's cells and the patient's serum, is well established, incompatibility of the bloods still accounts for numerous avoidable accidents. It is probable that mistakes in selecting donors are attributable to poor technic in general and, in particular, to the use of grouping serums that are not sufficiently potent.

Many unfortunate accidents might easily be avoided if a cooperative organization of hospital, medical society and local health authority, such as that suggested, would undertake to teach recognized procedures for compatibility tests. The headquarters of such an organization might act as a local registry to which atypical blood could be sent for study and grouping and where transfusion accidents, so neglected at present, could be recorded and analyzed. Because of the widespread and increasing use of transfusion, these services, along with the control of the professional donor and measures to prevent transmission of disease by transfusion, are urgently necessary in the present American hospital program.

FROM AUTHORS' SUMMARY.

THE BLOOD TRANSFUSION BETTERMENT ASSOCIATION OF NEW YORK CITY: BLOOD DONOR BUREAU. DE WITT STETTEN, J. A. M. A. **110**:1248, 1938.

It is safe to say that the work that has been done by the Blood Transfusion Betterment Association and the recognition which it has received in the city of New York will stimulate the organization of services along the same lines elsewhere. Any city of considerable size with its suburbs or satellite towns can establish a similar organization without great difficulty and with the promise that it will function as usefully as the New York Association.

FROM AUTHOR'S SUMMARY.

ESTIMATION OF PLASMA AND SERUM PROTEIN. B. M. KAGAN, J. Clin. Investigation **17**:369 and 373, 1938.

A new method for the estimation of the total protein in serum or plasma is presented. It is based on the linear relationship which exists between the specific gravity and the protein content. The specific gravity is determined by a new falling drop method, which is easy, time saving and capable of being carried out with extremely small quantities of blood. It provides a measure of the protein content with an accuracy which exceeds clinical requirements; it is about twice as accurate as the refractometric method. FROM AUTHOR'S SUMMARY.

A SILVER IMPREGNATION METHOD FOR RETICULUM. G. DE OLIVEIRA, Virchows Arch. f. path. Anat. **298**:523, 1936.

De Oliveira describes a silver impregnation method for which he claims the following advantages: It is rapid; it can be used and is best used for paraffin sections; it differentiates sharply between reticulum and collagen fibrils; it stains the finest intracellular reticulum fibrils, thus permitting study of the relationship of the cells to the fibrils. For the details of the method the reader is referred to the original article. O. T. SCHULTZ.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

ALFRED PLAUT, *President*

Anniversary Meeting, Jan. 26, 1939

ROBERT A. MOORE, *Secretary*

THE NASAL REACTION OF THE FERRET TO INFECTION WITH THE VIRUS OF EPIDEMIC INFLUENZA. THOMAS FRANCIS JR. (by invitation).

On intranasal inoculation of ferrets with the virus of epidemic influenza (PR8 strain) an orderly sequence of events occurs, involving the nasal mucous membrane. After twenty-four hours a moderate catarrhal reaction occurs, and after forty-eight hours almost complete destruction of the respiratory epithelium is seen. The olfactory epithelium is undamaged. Associated with the acute necrosis of the respiratory epithelium is an accumulation of exudate in the air passages and an acute inflammatory reaction in the submucosa.

In four to six days repair begins with the development of a transitional type of epithelium at the previous site of the respiratory epithelium. This gradually thickens and forms a true squamous epithelium, and by the twelfth to the fifteenth day the ciliated columnar cells are returning. In the fourth week a comparatively normal respiratory mucosa is seen, but some fibrosis of the submucosa remains. Occasional rests of transitional or squamous epithelium are interspersed through apparently normal areas.

During the period of repair, when the transitional and squamous epithelium is in prominence, reinoculation of the virus produces no reaction. The epithelium is resistant not only to virus but to physicochemical stimuli which normally destroy the entire mucous membrane of the nose. Thus there is observed an altered epithelium which maintains a refractory state or a state of immunity which bears no relation to ordinary immunologic concepts.

The state of complete refractoriness is temporary and gives way to a state of susceptibility to chemical injury. This return to susceptibility is associated with the reappearance of normal ciliated columnar cells. Nevertheless, one infection conditions the mucous membrane so that with subsequent infections the repair process is found markedly accelerated.

DISCUSSION

A. N. ROSEN: What is the character of the exudate?

THOMAS FRANCIS JR.: In the acute stage the exudate in the nose and nasal passages is essentially polymorphonuclear. Of course, there is sloughing of the epithelium along with it. In the submucosa the inflammatory reaction in the acute phase is usually predominantly polymorphonuclear, but in the animals which have received repeated inoculations and then show reaction to a subsequent inoculation the reaction in the submucosa is predominantly mononuclear.

ROBERT A. MOORE: Is it possible in ferrets to confer passive immunity so that there will be no clinical disease? If this should be possible, I wonder what would be the anatomic change in the mucous membrane if such an animal were inoculated intranasally with active virus.

THOMAS FRANCIS JR.: On occasion, if one is lucky, one may have an animal which appears to become immune by that procedure. On the other hand, the majority of animals have to be given relatively large amounts of serum, and even

then one may observe a certain amount of nasal reaction. The same thing is true in vaccinated animals. One may vaccinate them and induce production of the antibody and yet not have full protection from the nasal reaction, but those are studies which are not really completed.

IRVING GRAEF: Apropos of the remarks about the apparent immunity of the reparative respiratory epithelium, I am wondering whether or not during the earliest period of sloughing induced by zinc sulfate the virus in the nose may penetrate the mucosa and perhaps invade the olfactory nerves more readily. Is there any evidence of invasion via the mucosa in the first twenty-four to forty-eight hours?

THOMAS FRANCIS JR.: One has no way of detecting that from the point of view of the olfactory nerve with the PR8 strain of virus. Stuart-Harris and I tried in certain experiments, which are still not complete, the reverse procedure of instilling zinc sulfate into the nose, observing the damage and watching for the stage of repair to find out whether we could get resistance to develop. It appeared we were not getting complete immunity but a modified disease. There is a factor which we cannot control entirely. While we attempt to keep the zinc sulfate from getting into the lungs, we cannot prevent the possibility of the virus getting into the lung, and since it is adapted to the lung, one always has that as another source of infection. When one sees the type of damage which occurs with the virus alone in the acute stage, or with zinc sulfate alone in the acute stage, one thinks that the entire structure would be more susceptible to any type of infection. On the other hand, after five or six days it seems much more resistant to any type of infection.

MILTON HELPERN: Does the repair after the application of zinc sulfate occur more rapidly in an animal which has recovered from a previous inoculation of virus than in an uninfected animal?

THOMAS FRANCIS JR.: I cannot answer that. We had too few animals treated in that way to decide, but we had a distinct feeling with zinc sulfate that there were more islands of undamaged tissue left than with the virus. Whether that was simply due to chance or not I do not know.

MILTON HELPERN: I wonder if the difference in reaction to zinc sulfate as shown by an uninfected animal and an animal during the stage of repair is not due to the fact that columnar epithelium is less resistant than stratified epithelium to a corrosive.

THOMAS FRANCIS JR.: We appreciate that, and we also think it was probably a factor in resistance to the virus. I do not believe that this is simply a mechanical barrier. I think it is a question of the selective action of the virus or of a chemical on certain types of cells. In the repair process, which was quite striking around the eighth to the tenth day, when we had the most striking stratified epithelium, we got resistance not only in the respiratory area but also in the olfactory area, and I do not know how to explain that unless the virus had done something to the olfactory cells but not anything to cause great damage. When on the fifteenth day we added the zinc sulfate, the first cells to be destroyed were the ciliated columnar cells.

N. CHANDLER FOOT: Have you tried secondary infection with pyogenic cocci to see whether the epithelium which becomes resistant to the virus has become more susceptible to the pyogenic cocci which are observed in connection with the usual secondary infections of influenza?

THOMAS FRANCIS JR.: We have not done that. We have had this experience: We had animals which were carriers of Streptococcus, and we inoculated them with the virus; in those animals disease and death occurred, much more rapidly with mediastinitis, pericarditis, pleurisy with effusion and septicemia. We had in the present group a certain number of animals which had a chronic bacterial infection superimposed on the virus infection, and in these animals the undifferentiated epithelium was apt to persist much longer, and the ciliated epithelium was slower in returning. In one, particularly, the whole side of the nose was in what might

be thought of as the twelfth-day stage of repair, whereas the other side was normal, and in that animal there was distinct pus in the antrum.

A. B. SABIN: How much of the respiratory epithelium is damaged by the virus?

THOMAS FRANCIS JR.: In the respiratory epithelium we rarely see anything remaining. Occasionally we see a small island, but the surprising thing is how complete the damage is, particularly when one thinks of the structure of the anterior turbinate bone. That is one of the differences between the virus and the zinc sulfate. There is always much more complete damage with the virus than with the zinc sulfate, so that one can say that 99 per cent of the respiratory epithelium was destroyed by the virus; the destruction was almost complete.

A. B. SABIN: I ask that because these studies have a definite bearing on the anatomic basis of tissue immunity. If this virus destroys almost all the susceptible cells, it does not share this property with many others. Most other viruses usually leave large portions of susceptible tissue anatomically unaffected. If immunity were limited to the cells which had been attacked and had then undergone an anatomic change, there would be no immunity in the uninvolved tissues. Yet it is known that a whole organ or system may become immune when only a few of its cells have been directly affected by the virus, under conditions in which humoral antibodies play little or no role. One is led to assume, therefore, that in addition to the recognizable anatomic changes, certain other, more subtle changes must occur in all the susceptible tissues to account for their acquired resistance to infection with a specific virus. That holds perhaps not only for infectious agents but also for physicochemical agents. I might say from personal experience with zinc sulfate instilled intranasally in monkeys that while there is early injury to some of the cells of the olfactory mucosa, large portions of it show no sign of damage, and within a week all of it may appear normal; yet for a period of several months that mucosa remains resistant to infection with the virus of poliomyelitis, indicating that resistance cannot be attributed to the disappearance of, or to the anatomic change in, the susceptible cells.

THOMAS FRANCIS JR.: I think that is true. The fact is that following inoculation the PR8 strain destroys primarily the respiratory epithelium and leaves the olfactory epithelium untouched, and yet after ten to twelve days the zinc sulfate, which would normally wipe out all the epithelium, does not damage it. This is in the absence of any change in the olfactory epithelium. In the lung a similar state of affairs occurs. We did not get complete involvement of the entire lung, and yet the animals became resistant, and that is why we had the feeling that the tissue changes would not explain the entire picture of immunity in these instances. Up to a certain point we thought they would account for immunity in the absence of any serologic and immunologic reaction in the typical sense, but after that we would not rely on them.

So far as the observations on the monkey with the zinc sulfate, those changes are perhaps not quite so marked as in the present instances, because with ionization there is a pretty severe injury, and furthermore, when we used simple instillation we used it for as long as fifteen minutes; so it was not merely an application to the area. Instead of the coagulation type of necrosis which one sees following local application we saw a rather destructive wiping off of the epithelium.

CARCINOMA IN FROGS: ITS ETIOLOGIC RELATION TO A VIRUS AND ITS HABITS OF GROWTH IN VIVO AND IN VITRO (ILLUSTRATED BY A MOTION PICTURE). BALDUIN LUCKÉ (by invitation).

The leopard frog is commonly affected with an adenocarcinoma of the kidney which, like similar tumors in man and other mammals, invades and destroys the adjacent tissue of the organ in which it grows. Metastasis is commonly observed with tumors which have attained large size; dissemination usually takes place by way of the blood stream. These frequent metastases make the evidence for the

malignancy of this tumor complete; further, they throw doubt on the opinion, so often encountered in the literature, that tumors of cold-blooded vertebrates have little tendency to metastasize. Indeed, these studies and others in progress support the view that no matter in what species of animals tumors of the same kind occur they are much alike in behavior as well as in structure.

The carcinoma of the frog is a particularly interesting tumor as its nuclei commonly contain large acidophilic inclusions such as suggest activity of a virus. The results of transmission experiments make it very probable that this carcinoma is, in fact, induced by a virus. When the growth is inoculated as living fragments or a cell suspension into the lymph sacs, the cranial cavity or the abdomen, no significant local growth results, and the implanted material is gradually resorbed. However, in approximately 20 per cent of the frogs surviving inoculation for more than six months, tumors develop in the kidneys which are like the spontaneous neoplasms. The incidence far exceeds that in the controls.

Desiccated and glycerinated tumor injected into the abdomen gives the same results as inoculated living tumor; in somewhat over 20 per cent of animals surviving more than six months tumors of the kidneys occur.

In alien species of frogs, no tumors are produced by inoculation, either with living or with desiccated tumor.

These experiments indicate the probability that the carcinoma of the leopard frog is caused by an inclusion forming, organ-specific virus.

Thus in an amphibian a virus is seen to be capable of producing a malignant tumor. Since it is known that viruses produce certain tumors of birds and mammals, the conclusion follows that viruses may be a frequent cause of tumors throughout the animal kingdom.

Examination of nearly 1,000 control frogs gave very different results from those of the experimental series. During the first three months period after the inception of the corresponding experiments, slightly over 2 per cent had renal tumors. This incidence rose slightly to 6 per cent in the second three month period, and to 6.7 per cent in frogs surviving for more than six months. While this rise is far below the striking increase in the experimental groups, it may have considerable significance. There exists a real possibility that the neoplastic disease is transmissible from frog to frog. In captivity frogs are of necessity maintained under more crowded conditions than obtain in their natural environment, and confinement in the laboratory would favor not only direct contact but also indirect transference of various agents.

The characteristics of cancer growth have hitherto been studied chiefly by histologic methods, i. e., in material that has been fixed, sectioned and stained. The recent development of slit lamp microscopy makes it possible now to observe the habit of growth of living tumors. Bits of these tumors are implanted in the anterior chamber of the eye, where they soon establish themselves and where their rate of growth may be measured. The form of the tumor as well as the arrangement of the constituent cells may be observed through the cornea by means of the slit lamp microscope. Observation of many such transplanted fragments of carcinoma has led to the conclusion that the form which the growing tumor assumes depends on its immediate physical environment. Where the tumor grows out in the midst of the aqueous humor, not in contact with cornea or iris, there the habit of growth is characteristically tubular or papillary, the projections being hollow and cystic in some instances, solid masses of cells in others. If, however, the tumor grows in contact with an even surface, such as the cornea or the iris, then the form of growth is entirely different; broad membranes are formed which extend along and cover the cornea or the iris; such growths show no sign of tubule formation or, at most, abortive tubules, appearing late in the course of growth.

Study of tumors by the method of tissue culture has yielded much information concerning the differences between malignant cells and normal adult cells of the same type.

In the present experiments 32 frog tumors have been cultured by the roller tube technic of Gey and Lewis as well as by the ordinary hanging drop method.

Under these conditions budlike projections promptly grow from the tumor explant into the solid medium, where they form structures resembling tubules except for absence of lumen. The tubules are at first contained within basement membranes, but later the proliferating epithelial cells break through the basement membrane and spread out as thin fans of polyhedral epithelial cells. These fuse with other outgrowths of similiar character until the explant is entirely surrounded by a thin, flat layer of epithelium which shows no trace of differentiation into tubules or acini. The cells of the frog carcinoma are distinctly larger than those of most mammalian tumors, making the present material especially suitable for cytologic study.

In addition to direct observation, two cultures of the tumor were studied by cinematograph. This method not only affords a permanent record, but makes clearer the manner of outgrowth, the character of locomotion of the individual cells, as well as intracellular changes which occur so slowly as otherwise to escape detection.

DISCUSSION

JACOB FURTH: Dr. Lucké interpreted the increase in the percentage of tumors with increase in time of observation among the control frogs as due probably to spontaneous transmission. In this case the addition of tumor desiccate to the water might increase the incidence of tumors. Is it feasible to do the reverse—to raise frogs in sterilized water in attempts to obtain a tumor-free stock? To return to the first comment: Is it not possible that this increase in the number of tumors is due to increasing age of the frogs, and not to spontaneous transmission? This is a fundamental question. Thousands of chickens carrying filtrable tumors have been studied in many laboratories, but I do not know of a single instance of transmission of chicken tumor by spontaneous means.

BALDUIN LUCKÉ: It is entirely possible to do what you suggest, but practical difficulties are in the way. As one buys frogs from dealers, one gets frogs of all ages; in some twenty-odd thousand frogs which we have examined in our laboratory (we have divided them into groups of thousands) the incidence of spontaneous tumor is pretty steadily around 2 per cent in the different groups. I do not think that age has anything to do with increase in incidence among controls. I think it means that in some way the tumor is being transmitted. The fact that it does not occur in chickens simply means that it does not occur in chickens; it does not mean anything so far as frogs are concerned. Frogs suffer from all kinds of parasitic infection, and it is conceivable, though I do not offer this very seriously, that the virus is transmitted through parasites. What we are doing is keeping a large number of frogs, some of them having tumors, under as natural conditions as is possible, and these frogs are being kept together for as long a time as seems suitable. From time to time a group is examined, and the incidence of tumor is recorded. These experiments are as yet inconclusive.

IRVING GRAEF: Have you any observations on the effect of the desiccate or implants on tadpoles?

BALDUIN LUCKÉ: We have tried to implant desiccate as well as living material into tadpoles but have invariably failed to obtain tumors.

THOMAS J. FRANCIS JR.: May I ask about the old tradition that if a toad urinates on a man's hand he gets a wart? Do any of the tumor cells appear in the urine of these frogs, and, if so, would that be a means of tumor dissemination?

BALDUIN LUCKÉ: Tumor cells do appear in the urine. I have repeatedly punctured the bladder of a frog that had a tumor of the kidney and have found unquestionable tumor cells in the urine. Some of these are pretty badly broken up, but they are still cells of a tumor, and it is conceivable that through them a virus may be transmitted.

AMOUR F. LIBER: Is there any evidence of hereditary transmission?

BALDUIN LUCKÉ: To raise frogs is a difficult thing. It is easy to bring tadpoles to the frog stage, but from there on there is a very high mortality.

ALFRED PLAUT, *President*

Regular Monthly Meeting, March 23, 1939

ROBERT A. MOORE, *Secretary*

MULTIPLE PLASMOMA OF THE ILEUM AND COLON. CHESTER R. BROWN and AMOUR F. LIBER.

A colored man aged 57 was admitted to Lincoln Hospital on Nov. 27, 1938, complaining of "itching and leaking of purulent material from the rectum," said to have been present for from ten to fourteen years. The patient had lost 75 pounds (34 Kg.) in weight in the past three years. He said that there was a "sore on the penis" at one time, and that he received treatment for syphilis twenty years ago.

The man was emaciated and chronically ill; there was a blood-tinged purulent rectal discharge. Numerous polypoid firm masses were felt encircling the rectum about 3 inches (7.6 cm.) above the anus. The Frei test on the right arm showed a reddened wheal 2 cm. in diameter. The left arm (control) was negative. The Wassermann reaction was anticomplementary. The blood showed no significant changes. Pulmonary signs developed, and the patient died on Dec. 4, 1938. The clinical diagnosis was carcinoma of the rectum and bronchopneumonia.

Postmortem Examination.—Attached by broad bases to the external surface of the ileum throughout its entire course were numerous masses of yellow-white tissue, varying between 3 and 6 cm. in length and 2 and 4 cm. in breadth. The masses were considerably elevated above the serosal surface of the intestine and were quite firm to palpation. On section these were composed of firm, yellowish white tissue, of uniform consistency throughout, encircling about two thirds of the circumference of the ileum in localized areas. One of these nodules almost completely closed the lumen. Here the mucosa showed some superficial ulceration. The other masses did not encroach on the intestinal lumen.

The omentum and mesentery were adherent over a localized area of the hepatic flexure of the colon approximately 10 cm. in length. After removing the adhesions, a small localized abscess cavity was revealed, the base of which was formed by the exterior of the intestinal wall; in its center a necrotic opening could be followed down to the mucosa. Evidently these changes represented a localized chronic perforating lesion of the hepatic flexure. Section through this mass revealed dense yellow-white tissue involving all the intestinal coats and extending considerably above the serosal surface to form a polypoid mass with a sessile base.

The perirectal tissues showed infiltration of similar type, with marked induration. The mucosa was considerably elevated and firm, but showed no ulceration.

The mesenteric and portal lymph nodes were enlarged and of uniform soft consistency throughout.

Microscopic examination revealed the intestinal masses and lymph nodes to consist of cell infiltrations of uniform type throughout. These were solid sheets of plasma cells (about 80 per cent) and lymphocytes with varying degrees of fibroblastic induration. There were occasional macrophages. Amitotic division was frequent in the plasma cells. Polymorphonuclear cells were absent except in a small area localized to the perforation in the hepatic flexure. Reticulum cells were minimal. These collections infiltrated all the intestinal coats and the epiploon to form dense neoplastic-like masses. There was invasion of blood vessels by similar cell masses. No evident origin or localization could be noted in the lymphoid follicles of the mucosa, which were not enlarged.

The mesenteric fat was heavily infiltrated with similar cells, as were all the lymph nodes. The latter showed complete disorganization of the normal architecture. The sinuses and pulp formed solid cell masses. The capsule was invaded in many areas. Numerous periportal areas in the liver showed diffuse infiltrations of plasma cells and lymphocytes.

In the intestinal and lymphatic infiltrations, pleomorphism and giant cells were absent. Reticulum cell proliferation was minimal. The invasions of the lymph nodes and of the blood vessels and the periportal accumulations suggested metastatic lesions. The changes in no way resembled the histologic picture usually ascribed to the so-called benign intestinal granuloma or regional ileitis. Stains for spirochetes and tubercle bacilli were negative. We have found no case in which a condition similar to this was described as a visceral form of syphilis. The histologic observations do not resemble those of granuloma venereum.

Four cases somewhat similar to this one are reported in the literature:

Case 1 (Vasiliu, T., and Popa, R.: *Compt. rend. Soc. de biol.* **98**:738, 1928). Multiple ulcerated and nodular tumors were seen in the mucosa of the stomach and large and small intestine. The lymph nodes and the entire mesentery were invaded. Clumps of nodes compressed the ileum. Histologically, all the tumors were made up of plasma cells. The bone marrow was not examined.

Case 2 (Vallone, D.: *Ann. ital. di chir.* **9**:20, 1930). A 24 year old man was operated on because of chronic intestinal obstruction. The Wassermann test was negative. Fifteen centimeters of ileum was resected. The lumen was obliterated by a tumor composed of plasma cells and lymphocytes. The marrow was not examined.

Case 3 (North: A Case of Plasmocytoma of the Small Intestine; cited by Vallone). A woman aged 47 was operated on for intestinal obstruction. Thirty centimeters of ileum was resected. Sections showed marked infiltration of all the intestinal layers by plasma cells. The lesions were considered neoplastic.

Case 4 (Razzaboni: Di una rara lesione della parete intestinale infiltrato plasma-cellulare; cited by Vallone). There were multiple ulcerated tumors in the terminal part of the small intestine, the colon and the appendix, composed almost exclusively of plasma cells.

The origin of the plasma cell is highly controversial. Plasma cell tumors have been found in the nose and throat, lacrimal glands, conjunctiva, respiratory tract, skin, genitourinary tract and lymph nodes, without involvement of the bone marrow. Some are of malignant type (Masson, Jackson and Parker).

Although the marrow was not examined, we do not believe that ours is a case of medullary myeloma. In the latter disease the history and course are dissimilar. Metastases from medullary myeloma consist of pure plasma cells. We believe this to be a case of neoplastic multicentric plasmoma which may represent a variety of lymphosarcoma.

DISCUSSION

ALFRED PLAUT: There is a not very small group of intestinal lesions, more in the small than in the large bowel, which seem to be between tumor and granuloma. My colleagues and I have had 2 cases lately in our material, and I wonder whether the fact that the plasma cells predominate is something to differentiate Dr. Brown's case from others. In inflammatory lesions one does see sometimes a preponderance of plasma cells without these lesions being in other respects essentially different.

AMOUR F. LIBER: There is one feature of this case which would be difficult to explain on the hypothesis of chronic inflammatory granulomatosis, that is the presence of large collections of plasma cells in the lumens of blood vessels, in the outer coats of the affected parts of the intestine and also in the liver, where small blood vessels were packed with these cells. The cells in the lumens of the blood vessels are not part of a thrombus. They are not enmeshed in fibrin or platelets, and I am certain if one saw epithelial cells or cells which one might be inclined to attribute to a sarcoma in a corresponding situation one would not hesitate to speak of metastases going on by a vascular route.

POST-TRAUMATIC (BUT NOT POSTFRACTURAL) RAREFACTION OF LONG BONES. HENRY L. JAFFE.

It has been established on a roentgenographic basis that a blow, bump or twist to an articular or polyarticular region may be followed by pronounced rarefaction of the bones in the area in question. The instigating trauma need not have induced a fracture, and the rarefaction of bone may evolve even if the part continues to be used. This rarefaction is merely one element, however, in the complex of changes that evolve in the affected part. This complex includes rapid wasting of the local muscles and subcutaneous tissues and changes in the skin, which becomes cyanotically mottled, atrophic and scaly. In addition, the articular capsules of the part may shrivel so that articular function becomes considerably limited.

The post-traumatic syndrome is most familiar as localized in the hand or foot. Post-traumatic collapse of a vertebral body is undoubtedly another expression of it. However, material permitting adequate exploration of the pathologic-anatomic changes in this condition in these various localizations seems not to have become available.

The case being presented should contribute to knowledge of the pathologic nature of the condition in general. It also seems worth reporting in its own right as representing a rare localization of the disorder. Indeed, it hardly seems to be known at all that after trauma to a large joint region without fracture long bones, too, may undergo rarefaction. I have found in the literature reports of only 4 cases even roughly similar to the case being demonstrated. Anatomic material was not available in any of these, and in all the lesion seems to have been misdiagnosed clinically. In the case being demonstrated here, anatomic material did become available. This happened because the limb had been amputated through the upper third of the thigh on the mistaken assumption that a malignant tumor was present in the femur.

The subject, a man of 30, had injured his right knee in jumping off a wagon. He was unable to continue his work that day. Subsequently, he resumed work but had some difficulty because of painfulness and limitation of motion of the knee. Nine weeks after the injury there was a flexion deformity of the region. The latter was also tender to touch. Otherwise, the general health of the patient was good.

Roentgenograms taken about ten weeks after the injury showed profound and extensive modification of the lower half of the femur. There was complete obliteration of the spongy architectural pattern of the condyles. The condylar outlines showed notches in some places and in others were so vague that they could hardly be traced. Proximally to the condyles the rarefaction was still very pronounced. The patella, too, showed rarefaction, with irregularity and obscuration of its outline. In general, the tibia and fibula for some distance below their upper ends were also modified in this way. As noted, the changes in the femur were misinterpreted as reflecting the presence of a malignant tumor in that bone, and this is understandable in view of the ambiguous roentgenographic appearances. I myself have shown the roentgen pictures to several competent roentgenologists, giving them the pertinent facts about the case. All of them stated without equivocation that there was a malignant tumor in the femur. I mention this to show how natural the original erroneous interpretation was under the circumstances.

In the microscopic sections the bone rarefaction was also manifested in porousness of the compacta and meagerness of the trabeculae of the spongiosa. In the cortex large resorption spaces were found, filled with a loose fibrofatty connective tissue bearing numerous engorged blood vessels. The cortex also presented evidence that lively reconstruction had been going on in it. What is interesting, too, is the absence of osteophyte-like new bone deposition by the periosteum. In the spongiosa proper the intertrabecular marrow was fatty, somewhat abnormally fibrillar and slightly edematous. The original osseous trabeculae had been largely resorbed, but such trabecular fragments as had persisted also showed evidence of

reconstruction and regeneration. There was no evidence that these various changes had been preceded by aseptic necrosis.

Some years ago Dr. William Boyd sent me tissue and copies of roentgenograms in this very unusual case and gave me his permission to use this material. For further details concerning this case, for the light it sheds on the general pathologic picture of post-traumatic rarefaction of bones of the hand and foot and of vertebral bodies and for a discussion of the possible pathogenic mechanisms, the reader is referred to an article by me published this year in *Radiology*.

SPONTANEOUS TUMORS OF RABBITS AND THEIR TRANSPLANTATION IN THE SAME AND IN ALIEN SPECIES. HARRY S. N. GREENE (by invitation).

During the past five years, 152 spontaneous tumors have been found and studied in a colony of rabbits which averages a population of approximately 800 adults. Mammary and uterine tumors have occurred in the largest numbers, and their frequent occurrence offers an unusual opportunity for pathologic investigation.

The uterine tumors and the acinar type of mammary growths arise without observable antecedent abnormal tissue changes. On the other hand, the papillary type of tumor of the breast originates as an apparently unrelated pathologic state and progresses through noninvasive neoplasia to cancer. In such cases repeated examination of mammary tissue shows the presence of a continuous disease process in which cystic disease, benign neoplasia and invasion occur as succeeding events in the breast.

Profound endocrinologic changes distinguish animals bearing the tumors and are present from the earliest stages of tumor development. Histologically, the changes are identical with those observed in animals subjected to long-continued treatment with estrone (theelin).

The tumors have been serially transferred through many generations of rabbits and have been successfully transplanted to the anterior chambers of alien species including the guinea pig, goat, sheep and hog. At autopsy, however, none of these animals showed endocrinologic changes similar to those observed in the animals bearing spontaneous tumors. It is suggested, therefore, that the endocrine changes are associated with the initiation of neoplasia and that the spontaneous tumors represent a natural analogue to the experimental induction of neoplasia with estrogenic substances.

DISCUSSION

AMOUR F. LIBER: The demonstration of the endocrine changes seems to be of particular significance in the rabbit if, as I believe, there is no evidence of a hereditary tendency to tumors in that species, as there is in mice. The demonstration by Lacassagne of the effect of estrogen in producing tumors of the breast was made in the males of tumor-bearing hereditary stocks, so that the demonstration of a corresponding effect in stocks presumably not bearing a hereditary factor for tumor production would be particularly important. I should like to ask whether the neuroma demonstrated was in the central or in the peripheral nervous system.

HARRY S. N. GREENE: In the peripheral nervous system.

AMOUR F. LIBER: It is striking that no tumors of the central nervous system are found in rabbits. Outside of those observed in human beings and a very small number reported in cats, tumors of the nervous system are almost unknown.

HARRY S. N. GREENE: I have made autopsies on 4,000 to 6,000 rabbits and have never seen a tumor of the stomach or of the central nervous system. Mammary tumors of the papillary type occur exclusively in Belgian hares and in Belgian-English hybrids of a single family group. The acinar type, on the other hand, occurs solely in a branch of the English breed and in hybrids derived from it. The uterine tumors are more widespread throughout the animal population but tend to occur in certain family groups. They are found with the greatest frequency in lines in which the incidence of toxemia of pregnancy is highest, and it is of interest that all animals bearing uterine tumors have recovered from one or more attacks of this disorder.

J. VICTOR: Is there any relationship between the sexual history of these animals and the occurrence of tumors? I wonder whether Dr. Greene tried the transplantation of uterine tumors to the uterus, and if so, was he successful? Another question is whether normal tissues may be transplanted into the eyes of alien species with any degree of success.

HARRY S. N. GREENE: I have not tried to transplant normal tissues to foreign species. Homologous transplants of normal tissue grow well for a period of time and offer a convenient means for studying the possibility of a virus relationship. Fragments of normal endometrium soaked in a filtrate of uterine tumor tissue have been transferred to the anterior chamber and, while growth occurred, histologic examination at different periods showed no evidence of neoplasia.

There is a definite relation between the sexual history and the occurrence of the tumors. The series of rabbits in which tumors of the breast occurred showed reproductive abnormalities, including sterility or reduced fertility, with diminished size of litter, increased number of deadborn young and poor maternal care, for at least six months before the appearance of the mammary lesions. These abnormalities occurred with increasing frequency as the disorder progressed, but the animals were capable of becoming pregnant and bearing litters up to the time of death. Animals bearing uterine tumors are usually infertile, but a similar reduction in reproductive index occurs during the six month period preceding clinical detection of the growths. The antecedent breeding history of animals bearing both types of tumor is also distinguished by frequent resorption of fetuses.

J. VICTOR: Have you made any studies on the secretion of estrogenic substances?

HARRY S. N. GREENE: We should like to do that, but we have been hindered by lack of funds and time.

ROBERT A. MOORE: As I understand it, a tumor of the rabbit transplanted into the eye of a rabbit gives metastases. Are there metastases when a tumor of the rabbit is transplanted into the eye of an alien species? Do you have any information concerning the source of the stroma in the alien species after several passages? Is there any way of determining whether the stroma is still rabbit stroma, or guinea pig stroma?

HARRY S. N. GREENE: I have been anxious to get the tumors growing in as many guinea pigs as possible and as a routine have killed animals for transfer purposes shortly after growth became evident. As a result, there has been no case in which a tumor has grown in a guinea pig for a period of time equivalent to that required before metastasis occurs in rabbits. Guinea pigs now living have borne the transplanted tumors for five months and are being held to determine whether or not metastasis will occur.

I have been interested in finding out whether the stroma of the transplanted tumor in these cases was guinea pig or rabbit tissue but as yet have not got to the point of actual investigation. The point can be determined without serologic tests. The Shope myxoma is specific for rabbit connective tissue, and if a tumor in a guinea pig's eye can be infected with this virus, the identity of the stroma as rabbit tissue will be established.

B. M. FRIED: In the early part of this century it was demonstrated by many observers that in a considerable number of cases an animal in which a transplanted tumor had developed and then receded was quite refractory to a second inoculation. The doctrine of resistance (or active immunity) to malignant disease was, however, vigorously combated and denied until Besredka came out with his conception of "local" immunity against some malignant tumors. Besredka found that the well known epithelioma of Brown and Pearce, which is almost invariably fatal when inoculated into the testicle of the rabbit, is harmless to the rodent when introduced intracutaneously. What is more, an animal in which the malignant tumor has been absorbed acquires a lasting immunity to subsequent inoculations with the carcinoma irrespective of the organ or the structure utilized. Dr. Greene has just demonstrated his interesting experiments with the spontaneous cancers

which he often found in aged rabbits. He succeeded in transplanting these tumors to homologous and heterologous animals. He noticed, too, that the transplanted tumors receded after having reached considerable dimensions. I wonder whether he has attempted to ascertain whether these animals with healed tumors became immune (or resistant) to subsequent inoculations with the same malignant neoplasm.

HARRY S. N. GREENE: Simultaneous inoculation of both eyes or of one eye and a testicle gives rise to growth in both locations. If the second inoculation is delayed for thirty-five days, growth still occurs, but if the second inoculation is delayed for one hundred and thirty-five days, reinoculation is unsuccessful. It is assumed that a refractory phase develops in response to the continued presence of growing neoplastic cells. It seemed possible that the long delay of metastasis in animals bearing spontaneous tumors, in spite of the presence of neoplastic cells in the blood stream from an early period of tumor development, might be related to a similar phase. To test this possibility, tumor material derived from one of the serial eye generations was transferred to the anterior chambers of animals bearing spontaneous uterine growths of the same nature. The success of transplantation was apparently directly related to the age and size of the spontaneous growths. "Takes" occurred and subsequent growth was rapid in all instances in which the spontaneous tumor was old and large. On the other hand, complete failure or extremely slow-growing nodules which were no more than doubled in size after six months of growth followed transfer to animals with small, early uterine tumors. Histologically, the small, slow-growing nodules were characterized by an abundance of stroma and a well differentiated epithelial structure, in direct contrast to the appearance of transplants in the eyes of normal animals. It is conceivable, therefore, that a refractory phase may arise in response to the presence of the primary growth in spontaneous cases and possibly account for the long delay of metastasis.

SARCOMA OF THE TRACHEA. TOBIAS WEINBERG (by invitation).

Two cases of sarcoma of the trachea are reported, increasing the total of reported cases to 34. Both occurred in men, aged 50 and 34, respectively. The former gave a clinical history covering five years, and the latter one covering fourteen months. The first patient's lesion was diagnosed at biopsy as "suggestive of mixed tumor of the salivary gland type." The postmortem specimen showed the characteristics of myxosarcoma. Reexamination of all the biopsy specimens showed gradual transition into that of the postmortem picture, and because of this the possibility was considered of a unilateral development of a mixed tumor into a myxosarcoma. The second patient's tumor was typical spindle cell sarcoma. The tumors in both patients were situated both endotracheally and peritracheally, the myxosarcoma destroying the cartilages in its path.

Sarcoma of the trachea is slow growing. It may be present for a long time before producing clinical manifestations. The latter are apparently caused primarily by collapse of the wall, due to destruction of the cartilages involved. The exaggeration of symptoms is usually due to increase in the endotracheal growth of the tumor mass itself.

Usually the tumor is situated in the upper third of the trachea and arises from the posterior and lateral walls. It occurs in the earlier decades of life, and its occurrence is equally divided between the sexes. Most of the cases described in the literature have been instances of the spindle cell variety; 2, however, have been cases of myxosarcoma.

The tumor is only locally malignant, metastases being rarely reported and then being present only regionally. Aspiration metastases to the lung and carina were present in the second case reported.

Accordingly, death is not induced by the inherent malignancy of the tumor but rather by a complex mechanism involving the respiratory and cardiovascular systems. The tracheal stenosis produced by these tumors leads to emphysema and subsequently to right ventricular hypertrophy and ultimate cardiac failure.

ALFRED PLAUT, *President*

Regular Monthly Meeting, April 27, 1939

ROBERT A. MOORE, *Secretary*

XERODERMA PIGMENTOSUM. D. S. D. JESSUP.

A case of xeroderma pigmentosum which had reached the tumor stage is reported. The patient, a boy of 12 years, and his brother two years older, who also has the disease, have been under observation for eight years. They are the only children of their parents, who are not related. The family history is noncontributory. The tumor formations are confined to the face and have been treated by desiccation and trichloroacetic acid, and more recently by excision. Pathologic examinations have shown four squamous cell carcinomas and one basal cell carcinoma. At present the patient's nutrition is good, and there is no anemia. Besides excision of the tumors, treatment has consisted in maintenance on a high caloric diet with cod liver oil and intramuscular injections of liver extract. There has been no evidence of metastasis to the lymph nodes and in considering this disease of infancy and childhood it is interesting to note that the literature does not show any reports of metastasis to lymph nodes from cutaneous carcinoma in cases in which the diagnosis was verified by microscopic examination. Death is usually due to malnutrition and anemia, and, of the 3 patients reported as having come to autopsy, only 1 presented evidence of visceral metastasis, and this was a melanosarcoma of the liver, which was considered secondary to a nonpigmented sarcoma of the face.

The paper will be published in the *American Journal of Cancer.*

ACQUIRED PARASTERNAL DIAPHRAGMATIC HERNIA ON THE RIGHT. RUDOLF A. COLMERS (by invitation).

An obese woman 77 years old died with a clinical diagnosis of cardiovascular disease. There was a history of repeated abdominal pain on the right when the patient was in her forties for which appendectomy and later cholecystectomy were performed without lasting beneficial results. At the age of 57 she underwent an operation for a femoral hernia. A few years later she began to have bronchitis with marked dyspnea and cardiac insufficiency. At this time the first roentgen examination of the chest was made and revealed a peculiar shadow in the right lung field. No definite diagnosis was made, but neoplasm was considered. In the following terminal fifteen years of her life the roentgen findings remained essentially the same. A diagnosis was never established. At no time was there any barium sulfate given to aid roentgen examination. The significant findings at necropsy were as follows:

The diaphragm was at the level of the fifth rib on either side. Behind the xiphoid process and slightly to the right, at the site of the muscle-free space of Larrey, there was a round hole, 5 cm. in diameter, on the under surface of the diaphragm. This hole was the orifice of a hernial sac which extended upward, outward and slightly posteriorly into the right thoracic cavity, reaching the level of the third rib anteriorly. It was entirely covered by pleura. Its anterior wall was formed by rather loose connective tissue; its posterior wall, by the tendinous portion of the diaphragm. Its inner surface was lined by peritoneum. In this hernia, a loop of transverse colon, part of the great omentum and the upper part of the round ligament of the liver were found. The contents of the sac were easily removed and showed no signs of vascular disturbance. The hernia displaced the markedly enlarged heart to the left. There were signs of a healed mild adhesive pericarditis and considerable adipositas. Most remarkable was the middle lobe of the right lung, which was reduced to a thin strip of fleshy tissue. It contained a calcified nodule, apparently a healed primary tuberculous focus. Its bronchus was of normal caliber, but about 1 cm. from its root it showed an

upward kink, and from this point on its lumen was collapsed. Microscopic examination revealed advanced atelectasis and fibrosis, with much coal pigment present. Corpora amylacea were found in some of the alveolar spaces. Elastic fibers were abundant and were present also in the collapsed alveolar walls. The anatomic diagnosis, therefore, is true parasternal hernia on the right, with displacement of the heart to the left. The right middle lobe showed compression atelectasis.

Parasternal hernia on the right is relatively infrequent. According to Hedblom, the instances form about 3 per cent of all cases of diaphragmatic hernia. In the literature there are reports of about 60 cases, many of which include only roentgen findings, recent necropsy reports being relatively rare. The instance reported here is the only recorded case of right-sided parasternal diaphragmatic hernia in which there was shown acquired total atelectasis of the middle lobe of the right lung. This is of importance because of the light that it throws on the causes of the condition.

It is believed that the parasternal diaphragmatic hernia in this case developed during adult life, for the following reasons:

1. The patient falls in a group of patients whose age and constitution are generally considered to predispose to parasternal hernia.

2. The clinical symptoms referable to the hernia did not appear until the patient was middle aged.

3. The many elastic fibers in the alveolar walls of the atelectatic portion of the lung prove that this compression atelectasis developed in extrauterine life.

4. The abundant coal pigment in the atelectatic lobe shows that this condition must have been acquired rather late in life, and therefore the time of formation of this hernia narrows down at least to adult life.

As this case in every respect fits into the classic picture of parasternal diaphragmatic hernia and as the time of onset is clear, strong support is lent to the correctness of the theory that such a hernia is acquired in extrauterine life.

DISCUSSION

HERBERT J. WIENER: I should like to compliment Dr. Colmers on his careful preparation and excellent presentation of this case. It is a case I knew very well and followed for a good many years. From the clinical angle it is of considerable interest that when the first roentgenograms of this patient's chest were taken and this peculiar shadow appeared coincident with the clinical symptoms of rather severe bronchitis, it was debated whether there might not be an encapsulated intralobar effusion, and it was suggested and favored by one consultant that a paracentesis be done. Obviously, that would have been an unfortunate procedure, because it would likely have led to an infection of the area punctured. The symptoms really could not be attributed to anything but a pulmonary involvement from the clinical study, which was made by a number of excellent men. No one even considered the possibility of a diaphragmatic hernia.

R. A. COLMERS: I talked over the roentgen findings with Dr. William H. Meyer, our radiologist. He said that it was impossible to make a diagnosis of diaphragmatic hernia from the flat plate but that this condition should be one of the first things to be considered. As diaphragmatic hernia occurs on the right side in only about one sixth or one seventh of all the cases physicians do not generally take it into consideration in making a differential diagnosis. Parasternal hernia, however, is as frequent on the right side as on the left.

PULMONARY ATRESIA AND "TETRALOGY OF FALLOT." LOUISE H. MEEKER.

The case is that of a 54 day old boy whose weight at birth was normal, 9.2 pounds (4,173 Gm.). There were no obvious abnormalities. The baby was cyanotic from birth and unable to live outside an oxygen tent. There was a history of tremors shortly after birth.

The family history was not important. The patient was the third living child; the 2 others were twins; another child had died on the third day. The patient was admitted to the hospital at the age of 14 days. The color was indigo blue on exertion. There was sucking in of costal interspaces on exertion. No heart murmurs were noted at any time.

The roentgen pictures showed the typical *coeur en sabot* considered by Rössle diagnostic of the tetralogy of Fallot, i. e., apex formed of right ventricle with notch and left ventricle apex above notch, defect in shadow of pulmonary artery and prominence of transposed aorta at right.

The autopsy showed no abnormalities. The lingula of the lung was very large. The heart weighed 58 Gm. The aorta, with three heavy semilunar cusps, was enlarged and in dextroposition, riding over the interventricular defect due to the absence of a membranous septum. There were complete atresia of the pulmonary artery, patent ductus arteriosus and pulmonary arteries dividing above this point. The right ventricle was much enlarged. The left side of the heart was hypoplastic.

Fallot considered that these anomalies constituted a disease entity and were the commonest cause of congenital cyanosis.

PROLONGED HYPERPYREXIA WITH NECROPSY. WARD J. MACNEAL, HENRY H. RITTER (by invitation) and S. MILTON RABSON.

A graduate nurse aged 26 had a surgical revision of the stump of her left index finger on June 21, 1938, for persistent low grade osteomyelitis. This operation was followed by extension of the infection, persistent severe headache, muscular incoordination and gradually rising temperature. Blood cultured on July 8 and 11 yielded a growth of Staphylococcus aureus. The temperature reached 106 F. at 8 p. m. on July 11. On the next day divided doses of stock staphylococcus bacteriophage were given intravenously to a total amount of 200 cc. At 8 o'clock that evening the rectal temperature reached 113 F.; at midnight it had fallen to 99.4. Subsequently the temperature rose again and varied from 104 to 109 for many weeks, with occasional excursions outside these limits up to 110, 111 or even 112. After a period of apparent improvement, the offending finger was disarticulated at its base on September 17. Following this operation the patient failed rapidly, acquired a severe colon bacillus infection of the urinary tract and after several attacks of respiratory failure died, October 9. Necropsy, performed after a delay of twenty-six hours, disclosed marked cerebral edema, pial hemorrhage in the left frontal and parietal areas, marked congestion of the right basal ganglions and of the pons, and in the left side of the cerebellum an irregular cavity occupying the major portion of the site of the dentate nucleus and extending to the right to involve the medial portion of the right dentate nucleus. Microscopically, the lining of the cavity consisted of disintegrating brain substance. Rod-shaped bacteria could be recognized in the brain tissue and were crowded together in its blood vessels. Inflammatory reaction was not recognized, nor could any evidence of a neoplasm be found.

This article will be published in full in the *Archives of Internal Medicine*.

DISCUSSION

MILTON HELPERN: I should like to ask Dr. MacNeal how long it was after the autopsy that the brain was sectioned, or whether it was sectioned at the time of the autopsy, because I think the cavities look suspiciously like the postmortem Swiss cheese holes one sees in brains which have remained in solution of formaldehyde for some length of time before sectioning, especially when the postmortem interval before autopsy is long.

ALFRED PLAUT: Was there any indication of cavities or pseudocavities in other parts of the brain? Many years ago my colleagues and I were confronted with the question of thermometer fraud in a patient. We then simply pushed the thermometer beyond the level of the sphincters, after having attached it to a string, and afterward pulled it out. Even the most skilful faker cannot do anything to a thermometer which is almost in the sigmoid.

WARD J. MACNEAL: The brain was not sectioned immediately, but at necropsy the lateral ventricles of the cerebrum were opened and the brain was then suspended in solution of formaldehyde. The cavity in the cerebellum was discovered only after fixation for about a week. There was no sign of a similar disintegrating process anywhere else. For that reason we feel that the evidence leaves something to be desired. The importance of this particular observation seems not to have been appreciated at the time. It was only on subsequent study that one realized that here was something of considerable importance. The same criticism holds true in regard to the observations on temperature. In spite of my urging that the temperature should be taken by mouth and rectum simultaneously, this was done for only about four days, and then there was definite rebellion and it was impossible to have it continued. Obviously one's interest in such a case may not be shared by every one concerned.

After a death one is not permitted to do anything to the body without the authorization of the superintendent's office, and although I was regarded as an intimate friend of the patient and her family, and all the members of her family in New York were willing to grant permission for an autopsy, the executive officer was unable to allow anything to be done until the legally responsible member in California had been consulted.

The whole subject is to my mind rather tragic, but if one reads the literature of genuine and fraudulent hyperthermia one finds it has a comical side. There is another paper, dealing with the literature, which will appear along with this one. Temperatures even above 160 F. have been reported, as some of the members may know.

EXPERIMENTAL TRANSMISSION OF ENDOCARDITIS LENTA. WARD J. MACNEAL and (by invitation) MARTHA JANE SPENCE and MARIE WASSEEN.

Endocarditis lenta, a specific infectious disease of man, has been transmitted to a large proportion of experimental rabbits by repeated intravenous injections of large doses of pure cultures of Streptococcus viridans isolated from the blood of human patients. The cardiac vegetations in the rabbits are large and easily recognized by gross inspection, and these lesions exhibit to a large extent the characteristic gross and microscopic features of the human disease. Large colonies of the streptococci are present. Apparently, however, the rabbit possesses a relatively high natural resistance to the infection, the endocardial lesions showing a real tendency to heal. This evident balance between the forces of infection and resistance would seem to make the rabbit a valuable experimental animal in which to study the phases of extension and of healing and also the influence of various therapeutic measures on such processes.

BUFFALO PATHOLOGICAL SOCIETY

ERNEST WITEBSKY, *President*

Joint Meeting with Buffalo Academy of Medicine, Nov. 23, 1938

SAMUEL SANES, *Secretary*

SPIROCHETAL JAUNDICE IN BUFFALO. NORMAN W. ELTON.

A fatal case of Weil's disease is presented which was recognized clinically because of the combination of azotemia, jaundice and hemorrhagic manifestations on the sixth day of illness. Death occurred on the tenth day of illness. A white guinea pig inoculated subcutaneously in the groin with urine obtained by catheterizing the patient's bladder on the day of admission to the hospital (sixth day of

illness) died thirteen days later with intense, spectacular jaundice, and multiple foci of interstitial hemorrhage in the lungs. Sections of the liver of this guinea pig prepared with the Levaditi stain exhibited great numbers of typical leptospiras in "c" and "s" forms, having tapered hooked ends. A second white guinea pig was inoculated in the same manner with urine aspirated from the bladder of the first guinea pig at autopsy on the latter animal, and died showing the same gross and microscopic picture on the tenth day.

This case constitutes the eighth reported to date in the United States in which death was proved to be due to leptospirosis icterohaemorrhagica, the third in which the disease was known to have occurred in a fish handler in this country and the first to occur in the Great Lakes port of Buffalo.

This article will appear in full in the *American Journal of Clinical Pathology.*

PATHOGENESIS OF TUBERCULOUS MENINGITIS. K. TERPLAN.

For the present discussion 23 cases of diffuse tuberculous meningitis in children, proved to be such by postmortem examination, were selected. In 6 of these tuberculomas were found, either single or in small numbers in different parts of the cerebral cortex, cerebellum and brain stem ganglions, varying in size from that of a lentil to that of a small hazelnut. Only in a single instance did the leptomeninx above the cortical tuberculoma show more pronounced meningeal tuberculosis. In all cases the typical anatomic picture of tuberculous meningitis was present, the exudate being especially dense in the basal cisterns and in the choroid plexus. In the 6 cases in which tuberculomas were found in the brain substance there were also huge hematogenous tubercles in the spleen, liver and lungs. In all cases in which only few miliary tubercles were seen in the liver, spleen or kidneys and almost none in the lungs there were no tuberculomas in the brain substance but rather uniform basal tuberculous meningitis. As in all cases the brain substance was carefully examined for tuberculous lesions, the findings in these cases do not support the view of Rich that in the majority of cases tuberculous meningitis follows direct extension of parenchymatous tubercles into the subarachnoid space. The findings support rather the work of Kment in Ghon's laboratory, who found that tuberculous meningitis with the typical basal localization is always associated with tuberculous lesions in the choroid plexus and with recent tubercles in the leptomeninx. In cases in which tuberculous meningitis had extended from a cortical tuberculoma, the process remained more localized and was most pronounced in the region of the parenchymatous tuberculoma. In those cases the typical picture of diffuse tuberculous meningitis was not present. That the escape of tubercle bacilli into the spinal fluid is most probably secondary to formation of recent tubercles in the leptomeninx had been stressed already by Askanazy and Korteweg, writing almost twenty years ago. The material in the present cases entirely supports the view that diffuse tuberculous meningitis with the classic basal localization of the exudate is either plexomeningeal or merely meningeal genetically. In addition the material included several instances in which in adults huge tuberculomas were found in the brain substance, infiltrating the leptomeninx, and huge meningeal tuberculomas of plaque-like appearance without evidence of diffuse tuberculous meningitis. In all these instances the plexus was normal and so also was the entire leptomeninx outside the area in which the tuberculomas were found.

PURULENT PERITONITIS FOLLOWING APPENDICITIS DUE TO A MEMBER OF THE TYPHOID BACILLUS GROUP, EBERTHELLA ŒDEMATIENS, DE ASSIS. ERWIN NETER.

Some bacteriologic and immunologic observations are presented from a study of a patient with purulent peritonitis due to Eberthella oedematiens, de Assis. This seems to be the first report of its kind.

The patient was a girl 18 years old, whose past history was without significance. For two days prior to admission she suffered severe pain in the right lower quadrant of the abdomen, associated with nausea and vomiting. On her admission to the hospital her temperature was 100.2 F. and her pulse rate 78. Examination revealed nothing pathologic except rigidity, spasm and rebound tenderness in the right lower quadrant of the abdomen, particularly over McBurney's point. The urine was normal; the blood showed 4,120,000 red cells, with hemoglobin 86 per cent, and 16,000 white cells, with 60 per cent polymorphonuclears, 18 per cent bands and 22 per cent lymphocytes. On operation diffuse purulent peritonitis and a gangrenous appendix without perforation were found. The appendix was removed and the abdomen drained. The patient made an uneventful recovery.

The micro-organism isolated from the peritoneal exudate of the patient on two occasions was a gram-negative motile bacillus, which produced acid within eighteen hours from dextrose, maltose and mannitol. At that time lactose was not fermented. No gas was formed in any of the substances tested. After continued incubation, however, acid (but no gas) was produced also from lactose. Gelatin was liquefied; indol was produced; litmus milk was acidified and clotted. The strain was not agglutinated by either anti-Eberthella typhi or anti-Shigella dysenteriae and paradysenteriae serums. The formation of indol clearly differentiated this micro-organism from Eberthella typhi, and, on the other hand its motility, from members of the Shigella group. The micro-organism isolated from the present patient corresponded to E. oedematiens (de Assis, A.: Estudos sobre o genero "Eberthella" Buchanan, 1918; Sobre dois novos bacillos pseudotyphicos: Eberthella tarda e Eberthella oedematiens, *Bol. Inst. Vital Brazil* **5**:3 [Sept.] 1928), and was found to be identical in its cultural characters with the two strains of E. oedematiens obtained from Dr. de Assis. When rabbits were inoculated intravenously with the strain described (a heat-killed as well as a living suspension), agglutinins readily developed. The antiserum caused large floccules with a formaldehydized suspension and very fine floccules with an alcohol-treated suspension. The serum prepared with the strain described here failed to agglutinate the two strains of de Assis. This finding supplements the observation of de Assis that his two strains were antigenically different.

The patient's serum ten days after the onset of the illness failed to agglutinate the strain of the patient; neither did the serum cause agglutination of the two strains of de Assis. Unfortunately, an examination of the patient's serum at a later time was not possible.

Further Investigations on the Pathogenesis of Hemorrhagic Necrotic Lesions in the Intradermal Pneumococcic Infection of Rabbits.

E. Witebsky, E. Neter and H. Ward.

There is a close resemblance between the hemorrhagic necrotic lesion occurring in the rabbit infected intradermally with pneumococci virulent for rabbits and the so-called Shwartzman reaction. In the experiments to be described we tried to correlate these two phenomena. The site in a rabbit in which pneumococci had been injected intradermally and which produced swelling and erythema could be transformed within three to four hours into a hemorrhagic necrotic lesion by injecting intravenously an agar-washing filtrate of a culture of Bacillus typhosus or meningococcus prepared according to Shwartzman's technic.

Pneumococci when examined for their capacity to produce active agar-washing filtrates were found to be negative. Active factors, however, could be obtained, though yet with irregularity, from the pneumococci themselves, especially when autolysates were used. The reason for the irregularity is probably based on the fact that the substance under investigation seems to be very labile as far as temperature and contact with air are concerned.

In our former experiments we were not successful in transforming the site receiving an intradermal injection of Shwartzman toxin or pneumococci, respec-

tively, into a hemorrhagic necrotic lesion by means of an intravenous injection of a suspension of living or heat-killed pneumococci. The difficulties, however, were overcome when pneumococci were grown in 2 per cent dextrose broth. One liter of dextrose broth was centrifuged, and the sediment suspended in about 25 cc. of saline solution. If a heavy suspension of pneumococci of that type is used, it is possible to transform a primary lesion of the type described into a hemorrhagic necrotic lesion by means of an intravenous injection of such a suspension: In one series of experiments intracutaneous injections of Shwartzman filtrates (obtained from meningococci) were given; in the second series rabbits were given intradermal injections of pneumococci. Twenty-four hours later a heavy suspension of pneumococci of type I was given intravenously. Within two to four hours the majority of these animals showed a hemorrhagic necrotic lesion at the site of the intradermal injection while the respective controls, not given intravenous injections, revealed no hemorrhagic necrotic lesion whatsoever. The addition of solution of formaldehyde U. S. P. in 0.4 per cent concentration seemed to kill pneumococci rapidly without apparently reducing their capacity to induce the reaction under investigation. While further experiments are necessary in order to obtain more regular results than have been possible so far, the positive observations seem already to add further proof to our original hypothesis, according to which septicemia may be not only a symptom but also an important factor in the pathogenesis of hemorrhagic necrotic lesions of pneumococcic infections.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

BAXTER L. CRAWFORD, *President*

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HERBERT L. RATCLIFFE, *Secretary*

THE ANNUAL GROSS LECTURE: FURTHER STUDIES ON THE PATHOGENESIS OF VASCULAR DISEASE. M. C. WINTERNITZ.

The objectives of the study of vascular disease which my associates and I have carried on for the past three years have included that of a clearer understanding of the structure and function of the blood vessel wall. Especial attention has been directed toward the mural blood supply in arteries and in veins and to the correlation of this with the many manifestations of vascular disease.

The basis for an understanding of the vascular pattern in the blood vessel wall was laid by the embryologic studies of Bremer. The demonstration of this pattern in normal vessels of adults is not possible in all instances, and the pattern varies in different animal species. It is rarely demonstrable in entirely normal arteries of young human beings. However, the vessel wall in its response to injury often demonstrates an abundant vascular network, visible because of its contained red blood cells and so arranged as to suggest that it is preformed.

The study of the nutrition of the intimal coat is complicated by the difficulty of establishing a definite norm for the thickness of this layer. However, rapid proliferation of intimal tissue is associated with a rich capillary plexus; the acute processes in the vessel wall which often lead to serious sequelae are accompanied by all the manifestations of exudation that are found in other situations, and the degenerative changes in thickened vessels are found to be associated with obliteration of preexistent vasa vasorum.

The vasa vasorum have three portals of entry into the blood vessel wall; the majority arise in the adventitia from larger branches and penetrate the medial

coat. Another group arise from the intimal surface as direct penetrating branches from the mouths of primary branches of the vessel. These enter the vessel wall and form an anastomotic plexus immediately around the orifice of the branch, from which secondary feeders are given off to the vessel wall in the region. A third group enter the vessel wall from the lumen and anastomose with the branches of the other groups.

With the use of clearing methods, it has been shown that hemorrhage, varying from very fresh and very small extravasations to very old and very extensive accumulations of blood, may be found in any of the coats of the artery and, indeed, of the vein also. Such hemorrhage may be bright red or dark red, orange, yellow and even green. As may be anticipated, there is an associated deposition of iron pigment. The macrophage may be seen in fresh lesions, laden with red blood cells as well as iron. These phagocytes contain much fat, stainable with sudan III. As many of these sudan-stained granules cannot be distinguished from red blood cells, which are also phagocytosed, the question of their relationship arises. A study of this problem has been made by injecting red blood cells as well as other substances into the peritoneal cavities of rabbits under varying circumstances. This work has led to the conclusion that, while macrophages derive their fat content in other ways, the evidence that both iron and fat may be derivatives of red blood cells ingested by them is all but incontrovertible. Confirmation is secured by the study of hemorrhage in other conditions—for example, thyroid adenoma or infarcts. Furthermore, disintegrated blood, in sinusoids within the vessel wall, often seems to provide a nucleus for calcification.

The causes for the variability in the vascularity of the different coats of the artery wall are no more clear than are those for the hemorrhage. The fact that vascularity is present in these coats, however, indicates that the blood vessel wall may react to irritants much as any other vascular tissue does, and that exudation of fluid, cellular elements and fibrin, as well as of red blood cells, may be encountered at different stages of disease of the vessel wall. The conditions which determine hemorrhagic exudate in the wall of the vessel must conform in general to those associated with similar exudate in other tissue.

From time to time one sees examples of disease that suggest strongly that infection plays a role in the production of vascular lesions. Particularly striking have been several cases of endocarditis due to Streptococcus viridans which occurred either in children, associated with patent ductus arteriosus, or in adults. In such cases there may occur lesions of the pulmonary artery and aorta, with or without intimal vegetations, which seem to have followed the adventitial vasa vasorum through the vessel wall to the intima. The changes may be both chronic and acute; indeed, it seems that a chronic process may give rise to the vascularity through which the acute process is mediated.

Lesions such as these have great similarity to those produced by Spirochaeta pallida and by the virus of rheumatic fever. The question arises whether syphilis and rheumatic disease of the blood vessel wall are as sharply differentiated from lesions due to other agents as has been believed. A boy of 18 years who died after a protracted course of chronic nephritis had focal areas of thickening in the coronary arteries. These were associated with sharp breaks of the elastica and muscularis of the media and vascularization of the vessel wall, extending through the medial coat from the adventitia. Serial examination of coronary vessels quite frequently shows such breaks in the media with more or less cellular infiltration of the adventitia and with thickening of the intima. Anatomic changes of these types, resembling the vascular lesions so characteristic of syphilis and rheumatic fever, make it essential to seek in infection, or perhaps, as a corollary, in allergy.

To illustrate the possible role of infection in lesions of the vessel wall, a series of experiments was devised. In the first place, it was found that the normal

femoral artery of man could be injected via the lumen of the neighboring vein. With this established, into the walls of veins of goats was injected a minute quantity of one of several organisms: Staphylococcus aureus, Streptococcus viridans, or a strain of Bacillus pyocyaneus isolated from a necrotizing intestinal arteritis encountered at the postmortem table. The extent of the lesion was determined after varying intervals.

The lesions in the wall of the vein varied from acute phlebitis, with or without thrombosis, to fibrous intimal plaques, depending on the organism used as well as on the duration of the experiment. Changes in the neighboring artery consisted of intimal proliferation, which was often quite rapid, exudation, with precipitation of fibrin in the vicinity of the internal elastic lamella, and, later, dense fibrous intimal thickening. Although in most cases the injection was made into a loose vascular tissue surrounding both artery and vein, it was sometimes possible to demonstrate what was apparently a vascular passageway for the infection from vein to artery. A lesion of the femoral vein and artery closely resembling these experimental lesions was encountered recently in a man at autopsy.

Book Reviews

Etude morphologique et biologique sur les flagellés intestinaux parasites des Muridés. Etude comparative des flagellés du Cobaye. By Léon Morénas. Pp. 234. Price, 60 francs. Paris: Masson & Cie, 1938.

In this monograph on the parasitism of the Muridae by intestinal flagellates the emphasis is on the biologic rather than on the morphologic studies. The hosts studied were Epimys norvegicus, Epimys rattus (rattus and Alexandrinus), Mus musculus, Apodemus sylvaticus, Pitymys subterraneus, Pitymys duodecimcostatus, Arvicola amphibius and Cavia porcellus. The genera Oïkomonas, Sphoeromonas and Selenomonas (of the Monadidae) are considered to be coprozoic, whereas the genera Monocercomonas, Trimitus and Eutrichomastix are thought to be young or transitional forms of Trichomonas. Enteromonas is considered to represent true parasites. Two new species of trichomonads are described: Trichomonas guiarti of the rat (which has been previously considered a Retortamonas) and Ditrichomonas lavieri from Pitymys subterraneus. A Trichomonas identical with Trichomonas parva of the rat was found in the field mouse, Arvicola amphibius, a rodent widely different from the rat but of similar habits. Chilomastix intestinalis was observed in the guinea pig and Chilomastix bettencourti in rats and mice, and Chilomastix caviae was found again in the guinea pig and restudied. Among the Diplomonadidae, Hexamita muris and Syndyomita intestinalis were observed. The only new finding in connection with the Giardiae is that the dwarf form of Giardia microti (from the field mouse) constitutes a new species.

Although the comparative frequence of infections in laboratory rats was higher than in sewer rats, the parasitic index in the latter was higher than has been generally admitted. Wild mice are parasitized only exceptionally, whereas Muridae of the fields (black rat, field mice) are parasitized nearly uniformly. In the latter case, however, the parasitism is usually single in an individual host. The appearance of parasitism in the young corresponds with the beginning of the weaning period and is correlated with the modifications of the intestinal flora. Hexamita and Giardia appear more precociously than Trichomonas and Chilomastic because of being less influenced by dietary modifications.

The conditions which determine the parasitism are the p_H, the diet and the flora. A progressive alkalinity following the small intestine was found to drop abruptly to acidity in the cecum. With the exception of Chilomastix (which requires an alkaline cecal content), the parasitism adapted itself so well to different values of p_H as to indicate that the latter plays only a minor determining rôle. Casein, the only protein in the diet, had a very unfavorable action on the development of Trichomonas. Whereas avitaminosis C in the guinea pig was without effect on the flagellate fauna, avitaminosis A in the rat brought about diminution and sometimes disappearance of the flagellates. This modification was thought to act through changes in the metabolism of mucus as well as in the p_H and the intestinal flora. Ratcliffe's observation that the existence of cecal flagellates seems to be incompatible with a flora rich in gram-positive bacteria was confirmed. This was supported also by cultural findings. The author believes that most of the flagellates in the Muridae and especially those in the Cavidae should be thought of as inquilines rather than as true parasites.

Les groupes sanguins. Leur application à la biologie à la médecine et aut droit. Professeur Ludwik Hirszfeld, directeur du départment de bactériologie et médecine expérimentale de l'Institut d'Hygiene de l'État, à Varsovie. Translated from Polish by Mme. Hanna Hirszfeld. Paper. Pp. 169, with 16 illustrations. Price, 30 francs. Paris: Masson & Cie, 1938.

The author of this book has played a significant part in the development of the knowledge of blood groups. Together with von Dungern, he worked out a hypothesis of inheritance of blood groups, a part of which is still valid, though another part was supplanted by the hypothesis of Bernstein. Von Dungern and

Hirszfeld discovered the subgroups A_1 and A_2. Later, during the war, Hirszfeld and his wife, the translator of the book, discovered the differences in the ethnic distribution of blood groups and thus initiated a new advance of research in anthropology.

The author states in the introduction that he wishes to be like the experimenter in attention to details and like the architect in seeing with the eyes of the mind the edifice of the future. He is singularly qualified to do both.

The book is intended for physicians, biologists and lawyers. It avoids technical details and can be easily understood by those who have a basic knowledge of the biologic sciences.

The first chapter, entitled "The Individuality of Blood," is a simple and clear introduction to the subject matter. It includes a historical review.

The following five chapters take up the inheritance of the group properties, the subgroups A_1 and A_2, the newer concepts of group O and the M, N, P, X and Q factors. Then follow a chapter on the exclusion of paternity and another particularly interesting one on the exclusion of maternity. The distribution of group factors in organs, secretions and tumors is treated in a separate chapter. In the discussion of the application of blood groups in criminologic investigation Hirszfeld stresses the sources of error in the interpretation of blood stains. In the succeeding brief but meaty chapters the following topics are dealt with: the blood groups in animals, the transmission of agglutinability (the so-called Thomsen phenomenon), destruction by enzymes, the role of the thermal amplitude, the concept of serologic constitution, the ethnic distribution and hypotheses concerning the appearance of blood groups. A touch of humor is introduced in the brief fourteenth chapter, on erroneous applications of the knowledge of blood groups to racial theorems which serve political purposes by appealing to national vanity. In the final chapter the usual view of the blood groups as static is replaced by a concept of dynamic gradations in the quantities of the blood group factors, the decrease of the A factor, for example, being accompanied by a parallel growth of property O. The role of mutations is presented convincingly.

The clarity of the presentation of complex problems, the synthetic and philosophic approach, the mastery of the handling, the emphasis on the essentials and the brevity make the reading of this book an exhilarating experience. It is heartily recommended to all who are interested in the subject.

Cancer with Special Reference to Cancer of the Breast. R. J. Behan, M.D., Dr. Med. (Berlin), F.A.C.S., Cofounder and Formerly Director of the Cancer Department of the Pittsburgh Skin and Cancer Foundation, Pittsburgh. Cloth. Pp. 844, with 168 illustrations. Price, $10. St. Louis: C. V. Mosby Company, 1938.

According to the preface, "this book is written primarily for the clinician who is seeking to enlarge his knowledge of the cancer problem." It is intended especially for the practitioner of medicine "whose practice is limited and whose collateral reading is not sufficiently extensive to familiarize him with the more important advances of cancer research and cancer treatment." It was originally written as a treatise on cancer of the breast, but since a comprehensive knowledge of cancer in general is required for the understanding of cancer of any single organ, it was extended to include consideration of many phases of cancer. The first 14 chapters (452 pages) are devoted to cancer in general, with special reference to breast cancer, and the remaining 15 chapers (361 pages), to treatment in various forms. The book is a compilation of the literature on cancer and not an authoritative presentation of well digested knowledge of the nature and of the diagnosis and treatment of cancer. References to the sources abstracted are given at the bottom of the page. The two chapters on the etiology of cancer, especially cancer of the breast, carry no less than 454 references, the chapter on pathologic physiology 379 and the chapter on irradiation 320. These figures indicate the scope of the compilation. The book contains a vast amount of facts and opinions about various aspects of cancer and no doubt will be of service, but mainly as a guide or index to original sources of information.